Appendices index

Appendix 1 Search strategies

1a. MEDLINE search strategy Database: Ovid MEDLINE(R)

1 exp Polycystic Ovary Syndrome/
2 Polycystic Ovar$.tw.
3 PCOS.tw.
4 PCOD.tw.
5 PCO.tw.
6 (stein-leventhal or leventhal).tw.
7 (ovar$ adj (scelerocystic or polycystic or degeneration)).tw.
8 anovulat$.ti,ab,sh,tw.
9 oligo ovulat$.ti,ab,sh,tw.
10 or/1-9
11 randomized controlled trial.pt.
12 controlled clinical trial.pt.
13 randomly.ab,ti.
14 randomized.ab,ti.
15 (crossover or cross over).tw.
16 placebo.tw.
17 RCT.tw.
18 trial.ti.
19 clinical trials as topic.sh.
20 or/11-19
21 exp animals/ not humans.sh.
22 20 not 21
23 fertil$.ti,ab,sh,tw.
24 infertil$.ti,ab,sh,tw.
25 subfertil$.ti,ab,sh,tw.
26 pregnan$.ti,ab,sh,tw.
27 exp ovulation induction/ or exp superovulation/
28 (ovulat$ adj2 induc$).tw.
29 (ovar$ adj2 stimulat$).tw.
30 superovulat$.tw.
31 or/23-30
32 10 and 22 and 31

1b. Embase search strategy Database: EMBASE.com

#1 'ovary polycystic disease'/exp OR 'stein leventhal syndrome'/exp
#2 (polycystic NEAR/2 ovar*):de,ab,ti
#3 pcos:de,ab,ti OR pcod:de,ab,ti OR pco:de,ab,ti
#4 leventhal:de,ab,ti
#5 (ovar* NEAR/2 (scelerocystic OR degeneration)):de,ab,ti
#6 'anovulation'/exp
#7 anovulat*:de,ab,ti
#8 (oligo NEAR/2 ovulat*):de,ab,ti
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10 'randomized controlled trial'/exp
#11 'controlled clinical trial'/exp
#12 randomized:de,ab,ti
#13 randomly:de,ab,ti
#14 trial:ti
#15 plecebo:de,ab,ti
#16 rct:de,ab,ti
#17 crossover:de,ab,ti OR (cross NEAR/1 over):de,ab,ti
#18 'clinical trial' OR 'clinical trials':de
#19 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20 #19 AND [animals]/lim NOT [humans]/lim
#21 #19 NOT #20
#22'infertility'/exp OR 'fertility'/exp OR 'subfertility'/exp
#23 infertil*:de,ab,ti OR subfertil*:de,ab,ti OR feril*:de,ab,ti
#24 pregnan*:de,ab,ti
#25 'pregnancy'/exp
#26 'ovulation induction'/exp OR 'superovulation'/exp
#27 (ovulat* NEAR/2 induc*):de,ab,ti
#28 (ovar* NEAR/2 stimulat*):de,ab,ti
#29 superovulat*:de,ab,ti
#30 #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
#31 #9 AND #21 AND #30

1c. Database: EBM Reviews - Cochrane Central Register of Controlled Trials
#1 [mh "Polycystic Ovary Syndrome"]
#2 (polycystic near ovar*):kw,ab,ti
#3 pcos:kw,ab,ti or pcod:kw,ab,ti or pco:kw,ab,ti
#4 leventhal:kw,ab,ti
#5 (ovar* near (scelerocystic or degeneration)):kw,ab,ti
#6 anovulat*:kw,ab,ti
#7 oligo near ovulat*:kw,ab,ti
#8 [mh anovulation]
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 randomized controlled trial:pt
#11 controlled clinical trial:pt

#12 plecebo:kw,ti,ab
#13 randomly:kw,ti,ab
#14 RCT:kw,ti,ab
#15 trial:ti
#16 crossover:kw,ti,ab or (cross next over):kw,ti,ab
#17 #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 [mh infertility]
#19 [mh fertility]
#20 [mh pregnancy]
#21 infertil*:kw,ti,ab
#22 fertil*:kw,ti,ab
#23 subfertil*:kw,ti,ab
#24 pregnan*:kw,ti,ab
#25 [mh "Ovulation Induction"] or [mh superovulation]
#26 ovulat* near induc*:kw,ti,ab
#27 ovar* near stimulat*:kw,ti,ab
#28 superovulat*:kw,ti,ab
#29 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28
#30 #9 and #17 and #29

Appendix 2 Characteristics of included studies

Study	Interventions	Age (mean)	BMI (mean)	DOI (mean years)	Inclusion criteria	Sample Size	Previous Treatment	Country	Setting	Maximum of treatment cycles	IUI or TI
Abuelghar 2013[1]	CC MF+CC	28.4 27.6	28.1 28.6	2.8 3.2	Overweight and obese infertile women with PCOS (Rotterdam criteria)	66	unknown	Egypt	single-centre	1	TI
Amer 2009[2]	CC LOD	29.1 28.1	26.1 26.2	1.8 2.1	PCOS (at least 2 of the following 3 features: clinical [oligo/amenorrhoea and/or Hyperandrogenaemia], biochemical [LH≥10 IU/l, LH/FSH ratio ≥2, testosterone>2.6 nmol/l or free androgen index (FAI) >5] and/or sonographic (polycystic ovaries) features.)	72	naive	UK	single-centre	6	TI
Amer 2015[3]	CC LET	NA	NA	NA	anovulatory women with PCOS	159	naive	UK	single-centre	7	TI
Atay 2006[4]	CC LET	26.2 27.1	25.8 26.1	2.4 2.2	Women with primary infertility and PCOS(oligo- or amenorrhoea and ovaries with at least 10 subcapsular cysts 2 – 10 mm in diameter	106	unknown	Turkey	N/A	1	TI

					and hyperechogenic stroma.)						
Ayaz 2013[5]	CC MF+CC	31.3 32.0	NA[a]	NA	PCOS (the presence of two of the three following criteria:1. Polycystic ovaries [either 12 or more peripheral follicles or increased ovarian volume, > 10 cm^3]. 2. Oligo or anovulation [irregular cycles, amenorrhea]. 3. Clinical and/or biochemical signs of hyperandrogenism [Acne, hirsutism, voice changes, and Clitoromegaly].)	42	unknown	Saudi Arabia	single-centre	6	TI
Aygen 2007[6]	CC LET	23.4 26.8	27.6 26.9	4.2 5.8	Infertility and PCOS (Rotterdam criteria)	10	unknown	Turkey	single-centre	6	TI
Badawy 2009[7]	CC LET	29.3 27.1	27.1 28.1	NA	Infertile women with PCOS (Rotterdam criteria)	438	unknown	Egypt	multi-centre	>1	TI
Badawy 2011[8]	CC TAM	25.8 26.2	29.9 30.5	1.5 1.4	PCOS (Rotterdam criteria)	371	unknown	Egypt	multi-centre	1	TI
Basirat 2012[9]	CC MF+CC	25.3 24.9	25.4 26.3	2.7 2.4	Infertile PCOS (Rotterdam criteria)	334	unknown	Iran	multi-centre	3	IUI
Bayar 2006[10]	CC LET	30.6 32.2	NA	3 5	anovulatory PCOS (Rotterdam criteria)	80	naive	Turkey	single-centre	>1	TI
Beigi 2006[11]	CC MF	NA	NA	NA	PCOS based on a history of hyperandrogenism, anovulation, oligomenorrhea	70	unknown	Iran	single-centre	6	TI

					or amenorrhea, diagnostic ultrasound and laboratory findings						
Boonstanfar 2001[12]	CC TAM	26.5 26.6	30.2 30.9	3.7 3.5	anovulatory women with infertility	95	naive	USA	single-centre	>1	TI
Boudhraa 2010[13]	CC MF+CC	30.7 30.6	29.8 30.0	2.5[b]	PCOS (Rotterdam criteria) with subfertility	63	unknown	Tunis	single-centre	3-6	TI
Cudmore 1966[14]	CC PB	24.6 24.6	NA	NA	A diagnosis of secondary amenorrhea of at least 2 year's duration; persistent oligomenorrhea with no more than 4 periods in 1 year; or anovulatory infertility (infertility of more than 2 years' duration in which anovulation was the only cause found)	22	unknown	Canada	single-centre	3	TI
Dasari 2009[15]	CC MF+CC	NA[c]	NA[d]	NA	Infertile PCOS (Rotterdam criteria)	40	unknown	India	single-centre	6	TI
Dehbashi 2009[16]	CC LET	24.3 23.6	27.1 27.5	2.3 2.0	PCOS (Rotterdam criteria)	100	naive	Iran	single-centre	1	TI
El-Biely 2001[17]	CC MF+CC	25.7 26.4	27.4 28.7	4.7 4.5	Infertile obese patients with PCOS (oligomenorrhoea, ultrasound findings of ≥ 10 ovarian cysts measuring 2-8mm around a dense stroma)	90	unknown	Egypt	single-centre	6	TI

Fleming 2002[18]	MF PB	28.6 29.2	34.2 35.0	NA	Women with oligomenorrhea or amenorrhea and PCO	42	naive	UK	single-centre	4	TI
Garcia 1985[19]	CC PB	27.6[e]	NA	NA	Anovulatory infertile women	49	unknown	USA	single-centre	5	TI
Homburg 2012[20]	CC FSH	29.4 29.8	25.7 25.1	2.1 2.1	anovulatory or oligo-ovulatory infertile women with PCOS (Rotterdam criteria)	302	naive	Netherlands, UK, Malta, Belgium, Argentina Colombia	multi-centre	3	TI/IUI
Jahan 2015[21]	CC LET MF	NA	NA	NA	PCOS	460	naive	Bangladesh	single-centre	6	TI
Johnson 1966[22]	CC PB	NA	NA	NA	Anovulatory women	65	mixed	USA	single-centre	1	TI
Johnson 2010A[23]	MF PB	29.5 29.2	38.0 37.6	3.3(2.4-5.9)[f] 3.4(2-5)[f]	anovulatory or oligo-ovulatory women with PCOS (Rotterdam criteria), BMI>32 kg/m^2	65	mixed	New Zealand	multi-centre	6	TI
Johnson 2010B[23]	CC MF MF+CC	28.2 28.9 29.2	26.2 26.5 26.9	2(1-3)[f] 1.5(1-4)[f] 2(1.5-5)[f]	anovulatory or oligo-ovulatory women with PCOS (Rotterdam criteria), BMI≤32 kg/m^2	106	mixed	New Zealand	multi-centre	6	TI
Kar 2012[24]	CC LET	26.3 26.3	26.0 25.9	3.1 3.1	infertile PCOS (Rotterdam criteria)	103	naive	India	single-centre	1	TI/IUI

Kar 2015[25]	CC MF MF+CC	25.8 25.2 26.6	26.5 24.5 27.2	2.8 1.7 2.5	PCOS (Rotterdam criteria), with the primary complaints of infertility and oligomenorrhea	105	naive	India	single-centre	6	TI
Karimzadeh 2007[26]	MF PB	27.2 28.6	28.8 29.5	5.6 6.2	PCOS (Rotterdam criteria)	200	unknown	Iran	single-centre	3	TI
Karimzadeh 2010[27]	CC MF MF+CC	27.5 27.3 27.3	27.2 27.2 28.0	4.1 3.9 4.6	infertile PCOS (Rotterdam criteria)	268	unknown	Iran	single-centre	6	TI
Keikha 2011[28]	CC LET	27.1 27.6	NA	2.9 3.0	infertile PCOS	116	naive	Iran	single-centre	1	TI
Khorram 2006[29]	CC MF+CC	28.0 28.4	38.8 35.3	NA	PCOS (anovulatory or oligo-ovulatory cycles, polycystic ovaries on a baseline ultrasound, hyperandrogenism) and infertility	31	naive	USA	single-centre	1	TI
Leanza 2014[30]	CC MF+CC	26-34[g]	NA	NA	PCOS (typical ultrasound situation, oligomenorrhea/amenorrhea, hyperandrogenism) with above 3 years of infertility, BMI>27.5	56	naive	Italy	single-centre	3	IUI
Legro 2007[31]	CC MF MF+CC	27.9 28.1 28.3	36.0 35.6 34.2	3.5 3.3 3.4	infertile women PCOS (oligomenorrhea and hyperandrogenemia)	626	mixed	USA	multi-centre	6	TI

Legro 2014[32]	CC LET	28.8 28.9	35.1 35.2	3.5 3.4	infertile women PCOS (Rotterdam criteria)	750	mixed	USA	multi-centre	5	TI
Liu 2015[33]	CC LET	NA	NA	NA	PCOS patients who have conception desire	134	unknown	China	single-centre	>1	TI
López 2004[34]	CC FSH	29(23-38)[f] 30(22-39)[f]	22.3 21.9	3(1-8)[f] 3(1-8)[f]	anovulatory infertility due to PCOS (Rotterdam criteria)	76	naive	Spain	single-centre	3	TI
Lord 2006[35]	MF PB	27.8 30.6	33.7 36.4	NA	PCOS (anovulation and a raised free androgen index (FAI) >5.0)	44	unknown	UK	single-centre	3	TI
Lorzadeh 2011[36]	CC LET	26.1 28.2	25.4 24.2	NA	PCOS (based on the chronic anovulation and clinical/lab-based hyperandrogenism), age <35, No successful pregnancy after one year of weekly (2-3 times) sexual contact without contraception.	100	unknown	Iran	single-centre	>1	TI
Maged 2015[37]	CC MF+CC	26.0 25.8	27.3 27.7	2.8 2.8	PCOS (Rotterdam criteria)	80	unknown	Egypt	single-centre	3	TI
Mobusher 2014[38]	CC LET	24.3 24.3	25.9 25.9	3.1 3.2	PCOS (Rotterdam criteria) and infertility	100	naive	Pakistan	single-centre	1	TI
Moll 2006[39]	CC MF+CC	28.4 27.9	27.8 28.5	1.3 1.6	PCOS (Rotterdam criteria), all women with chronic anovulation and polycystic	225	naive	Netherlands	multi-centre	6	TI

					ovaries diagnosed by transvaginal ultrasonography						
Nazik 2012[40]	CC LET	27.8 25.6	25.9 24.7	4.4 3.4	PCOS (Rotterdam criteria)	64	naive	Turkey	single-centre	>1	TI
Palomba 2005[41]	CC MF	25.9 26.4	26.7 27.0	1.7 1.6	primary infertile anovulatory women with PCOS (NIH criteria)	100	naive	Italy	single-centre	6	TI
Raja 2005[42]	CC MF+CC	26.9 26.5	NA	4.9 4.2	Infertility and PCOS (the presence of polycystic ovaries on ultrasonography with two or more of the following criteria: Oligomenorrhoea [<6 cycles in preceding year); hirsutism; hyperandrogenism; Elevated LH or LH: FSH >2])	100	unknown	Pakistan	single-centre	6	TI
Ray 2012[43]	CC LET	29(20-35) [f] 28(19-35) [f]	28.5(24.2-33.6) [f] 28.8(23.2-34.6) [f]	2.4 2.2	Infertile PCOS (Rotterdam criteria)	147	unknown	India	single-centre	>1	TI
Robinson 2003[44]	CC MF+CC	NA	NA	NA	Women with a one-year history of infertility and diagnosed with hyperandrogenic oligoovulatory or anovulatory cycles as the sole etiology for their	48	unknown	USA	single-centre	6	TI

					infertility						
Roy 2012[45]	CC LET	26.5 26.1	25.4 25.8	5.8 6.4	infertility and anovulatory PCOS (Rotterdam criteria), BMI<28	212	unknown	India	single-centre	3	TI
Sahin 2004[46]	CC MF+CC	24.5(19-28) [f] 27(21-31) [f]	25.7(23.1-35.7) [f] 30.4(24.6-33.9) [f]	3.5(1-8) [f] 5(2-10) [f]	Primary infertility and PCOS (on the basis of three or more of the following criteria: polycystic ovaries on pelvic ultrasound examination, oligo/amenorrhoea, hirsutism, hyperandrogenaemia (total testosterone > 80 ng/dl and/or free testosterone > 3.18 pg/ml)) and elevated serum LH:FSH ratio (LH:FSH > 2))	21	unknown	Turkey	single-centre	6	TI
Santonocito 2009[47]	CC MF	27.4 28.1	27.1 26.8	1.7 1.6	infertility and anovulatory PCOS (Rotterdam criteria), BMI< 30 kg/m^2	36	unknown	Italy	single-centre	6	TI
Selim 2012[48]	CC LET	25.1 26.0	23.8 24.4	2.6 2.9	Infertile women with PCOS (Rotterdam criteria)	220	naive	Egypt	single-centre	1	TI
Seyedoshohadaei 2012[49]	CC LET TAM	24.7 26.9 25.4	NA	3.0 4.1 3.0	non-PCOS anovulatory infertility, and ovary without evidence of polycystic ovaries	150	unknown	Iran	single-centre	6	TI
Sharief 2015[50]	CC	25.3	27.8	2.3	primary infertility and	75	unknown	Iraq	single-	6	TI

	LET	26.1	28.1	2.4	anovulation due to PCOS (ultrasonographic polycystic ovaries plus one or more of the following: oligomenorrhoea, positive progesterone, withdrawal bleeding, hirsutism/acne, obesity, and Luteinizing hormone/Follicle-stimulating hormone (LH/FSH) ratio >2 or raised circulating androgen, normal thyroid stimulating hormone)				centre		
Sh-El-Arab Elsedeek 2011[51]	CC LET	25.0 25.0	29.2 27.7	NA	Nulliparous PCOS (Rotterdam criteria), BMI ≤35	124	unknown	Egypt	single-centre	1	TI
Tang 2006[52]	MF PB	29.7 29.8	37.6 38.9	4.5 4.9	anovulatory PCOS (polycystic ovaries on transvaginal scan, together with either oligomenorrhoea or amenorrhoea) and a BMI of >30,	143	naive	UK	multi-centre	6	TI
Vegetti 1999[53]	CC TAM	NA	NA	NA	Infertility and normogonadotropic anovulation	95	naive	Italy	single-centre	>1	TI
Williams 2009[54]	CC	NA	NA	NA	women with PCOS who are	55	unknown	USA	N/A	6	TI

	MF+CC				attempting to conceive.						
Zain 2009[55]	CC MF MF+CC	29.6 27.8 29.3	32.9 33.9 33.0	2.9 3.1 3.3	PCOS (Rotterdam criteria)	124	naive	Malaysia	single-centre	6	TI
Zeinalzadeh 2010[56]	CC LET	23.1 23.8	NA	2.6 2.4	PCOS (based on ultrasonography finding, oligomenorrhea and an increased LH/FSH ratio (>3))	107	naive	Iran	single-centre	1	IUI

(Abbreviations: CC, clomiphene citrate; PB, placebo or no treatment; LET, letrozole; MF, metformin; TAM, tamoxifen; FSH, follicle stimulating hormone; LOD, laparoscopic ovarian drilling; NA, not available; BMI, body mass index; DOI: Duration of infertility)

a. The percentages of women with BMI>25 in CC and CC+MF group are 71.4% and 56.7%, respectively.

b. The mean duration of infertility of all the participants (including both groups).

c. The percentages of women with age >31, 26-30 and 20-25 years are 8.3%, 41.7%, 50% in CC group and 18.8%, 43.8% and 37.5% in CC+MF group.

d. The percentages of women with BMI >25 and BMI < 25 are 37.5% and 62.5%, respectively.

e. in treatment group only

f. median (range)

g. range

Appendix 3 List of included studies

1. Abuelghar WM, Elkady OS, Khamees AA. Clomiphene citrate alone, in combination with metformin or in combination with pioglitazone as first line therapy in induction of ovulation in infertile women with polycystic ovary syndrome, a randomized controlled trial. Middle East Fertility Society Journal 2013;**18**(3):135-41
2. Amer S, Fakis A, Smith J, et al. Double blind cross-over randomized controlled trial comparing letrozole versus clomiphene citrate for ovulation induction in women with polycystic ovarian syndrome. Human Reproduction 2015;**30**:i96
3. Amer SA, Li TC, Metwally M, et al. Randomized controlled trial comparing laparoscopic ovarian diathermy with clomiphene citrate as a first-line method of ovulation induction in women with polycystic ovary syndrome. Human Reproduction 2009;**24**(1):219-25
4. Atay V, Cam C, Muhcu M, et al. Comparison of letrozole and clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation. Journal of international medical research 2006;**34**(1):73-6
5. Ayaz A, Alwan Y, Farooq MU. Metformin-clomiphene citrate vs. clomiphene citrate alone: Polycystic ovarian syndrome. Journal of human reproductive sciences 2013;**6**(1):15-18
6. Aygen EM, Güzel Z, Özgün T, et al. The use of letrozole for ovulation induction in infertile women with polycystic ovarian syndrome. Erciyes Tip Dergisi 2007;**29**(3):195-200
7. Badawy A, Abdel Aal I, Abulatta M. Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial. Fertility & Sterility 2009;**92**(3):849-52
8. Badawy A, Gibreal A. Clomiphene citrate versus tamoxifen for ovulation induction in women with PCOS: a prospective randomized trial. European Journal of Obstetrics, Gynecology, & Reproductive Biology 2011;**159**(1):151-4 doi: http://dx.doi.org/10.1016/j.ejogrb.2011.07.015.
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10. Bayar U, Basaran M, Kiran S, et al. Use of an aromatase inhibitor in patients with polycystic ovary syndrome: a prospective randomized trial. Fertility & Sterility 2006;**86**(5):1447-51
11. Beigi A. Randomized trial comparing clomiphene citrate and metformin as the first-line treatment for ovulation induction in polycystic ovary syndrome. Human reproduction (Oxford, England) 2006;**21**(Suppl):i129
12. Boostanfar R, Jain JK, Mishell DR, Jr., et al. A prospective randomized trial comparing clomiphene citrate with tamoxifen citrate for ovulation induction. Fertility & Sterility 2001;**75**(5):1024-6
13. Boudhraa K, Jellouli MA, Amri M, et al. [Indication of metformin in the management of hormonal dysfunction secondary to polycystic ovarian syndrome: prospective comparative study of 63 cases]. Tunisie medicale 2010;**88**(5):335-40
14. Cudmore DW, Tupper WR. Induction of ovulation with clomiphene citrate. A double-blind study. Fertil Steril 1966;**17**(3):363-73

15. Dasari P, Pranahita GK. The efficacy of metformin and clomiphene citrate combination compared with clomiphene citrate alone for ovulation induction in infertile patients with PCOS. Journal of human reproductive sciences 2009;**2**(1):18-22
16. Dehbashi S, Dehbashi S, Kazerooni T, et al. Comparison of the effects of letrozole and clomiphene citrate on ovulation and pregnancy rate in patients with polycystic ovary syndrome. Iranian Journal of Medical Sciences 2009;**34**(1):23-28
17. El-Biely MM, Habba M. The use of metformin to augment the induction of ovulation in obese infertile patients with polycystic ovary syndrome. Middle East Fertility Society Journal 2001;**6**(1):43-49
18. Fleming R, Hopkinson ZE, Wallace AM, et al. Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. Journal of Clinical Endocrinology & Metabolism 2002;**87**(2):569-74
19. Garcia CR, Freeman EW, Rickels K, et al. Behavioral and emotional factors and treatment responses in a study of anovulatory infertile women. Fertility & Sterility 1985;**44**(4):478-83
20. Homburg R, Hendriks ML, Konig TE, et al. Clomifene citrate or low-dose FSH for the first-line treatment of infertile women with anovulation associated with polycystic ovary syndrome: a prospective randomized multinational study. Human Reproduction 2012;**27**(2):468-73
21. Jahan S. Comparative study of efficacy among metformin, clomiphene citrate and aromatase inhibitor (letrozole) as the first-line medication for ovulation induction, achievement of pregnancy and live birth in Asian women with polycystic ovarian syndrome: A prospective trial. International Journal of Gynecology and Obstetrics 2015;**131**:E503
22. Johnson JE, Jr., Cohen MR, Goldfarb AF, et al. The efficacy of clomiphene citrate for induction of ovulation. A controlled study. Int J Fertil 1966;**11**(3):265-70
23. Johnson NP, Stewart AW, Falkiner J, et al. PCOSMIC: a multi-centre randomized trial in women with PolyCystic Ovary Syndrome evaluating Metformin for Infertility with Clomiphene. Human Reproduction 2010;**25**(7):1675-83
24. Kar S. Clomiphene citrate or letrozole as first-line ovulation induction drug in infertile PCOS women: A prospective randomized trial. Journal of human reproductive sciences 2012;**5**(3):262-65
25. Kar S, Sanchita S. Clomiphene citrate, metformin or a combination of both as the first line ovulation induction drug for Asian Indian women with polycystic ovarian syndrome: A randomized controlled trial. Journal of Human Reproductive Sciences 2015;**8**(4):197-201
26. Karimzadeh MA, Eftekhar M, Taheripanah R, et al. The effect of administration of metformin on lipid profile changes and insulin resistance in patients with polycystic ovary syndrome. Middle East Fertility Society Journal 2007;**12**(3):174-78
27. Karimzadeh MA, Javedani M. An assessment of lifestyle modification versus medical treatment with clomiphene citrate, metformin, and clomiphene citrate-metformin in patients with polycystic ovary syndrome. Fertility & Sterility 2010;**94**(1):216-20 doi: 10.1016/j.fertnstert.2009.02.078.

28. Keikha F, Shahraki Mojahed B. Induction ovulation in polycystic ovary patient with clomiphene citrate and letrozole. Iranian Journal of Reproductive Medicine 2011;**9**:46
29. Khorram O, Helliwell JP, Katz S, et al. Two weeks of metformin improves clomiphene citrate-induced ovulation and metabolic profiles in women with polycystic ovary syndrome. Fertility & Sterility 2006;**85**(5):1448-51 doi: 10.1016/j.fertnstert.2005.10.042.
30. Leanza V, Coco L, Grasso F, et al. Ovulation induction with clomiphene citrate and metformin in women with polycystic ovary syndrome. Minerva ginecologica 2014;**66**(3):299-301
31. Legro RS, Barnhart HX, Schlaff WD, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. New England journal of medicine 2007;**356**(6):551-66
32. Legro RS, Brzyski RG, Diamond MP, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. N Engl J Med 2014;**371**(2):119-29 doi: 10.1056/NEJMoa1313517.
33. Liu C, Feng G, Wang Q, et al. Comparison of ovulation induction protocol for women with polycystic ovarian syndrome: A prospective randomized trial. International Journal of Gynecology and Obstetrics 2015;**131**:E231-E32
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Appendix 4 List of excluded studies

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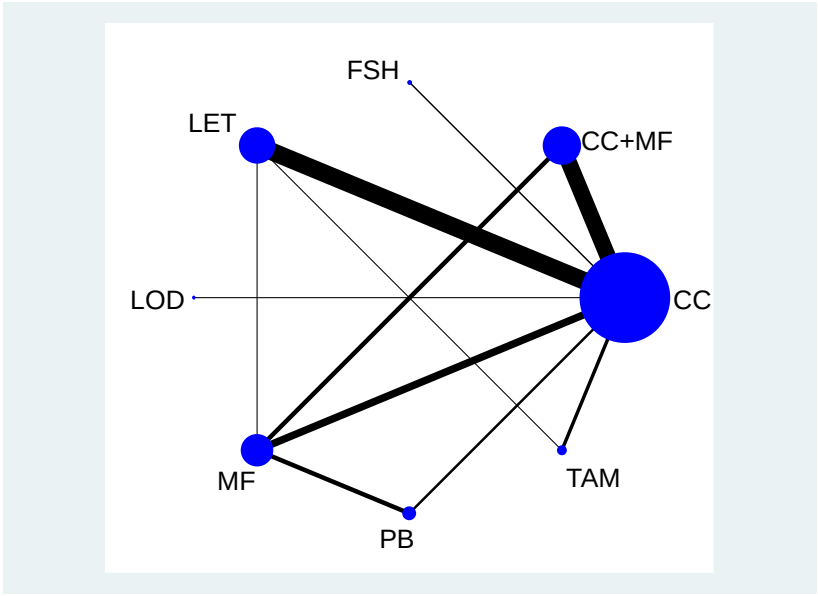
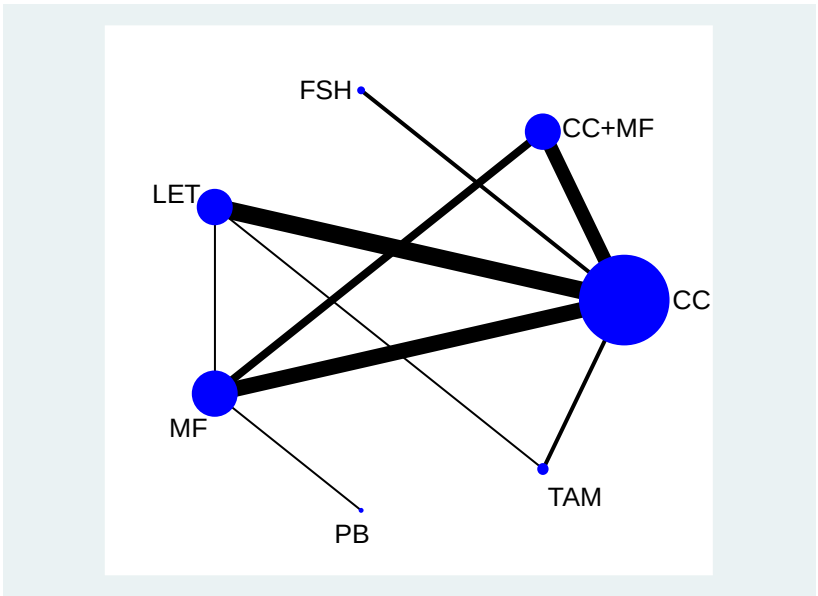
Appendix 5 (a-e) Network plots of eligible comparisons for five outcomes: pregnancy, live birth, ovulation, miscarriage and multiple pregnancy.
The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of studies including the respective interventions. (Abbreviations: CC, clomiphene citrate; PB, placebo or no treatment; LET, letrozole; MF, metformin; TAM, tamoxifen; FSH, follicle stimulating hormone; LOD, laparoscopic ovarian drilling)

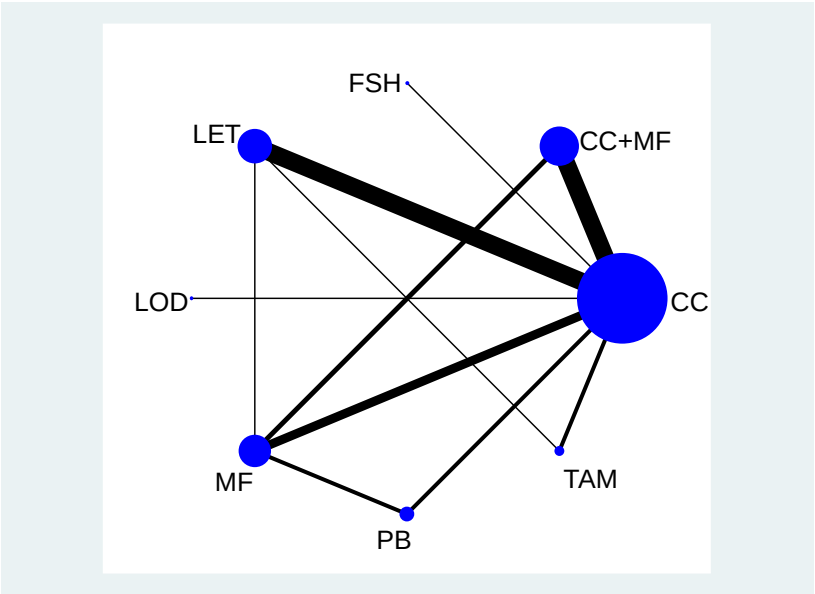
5a. Pregnancy



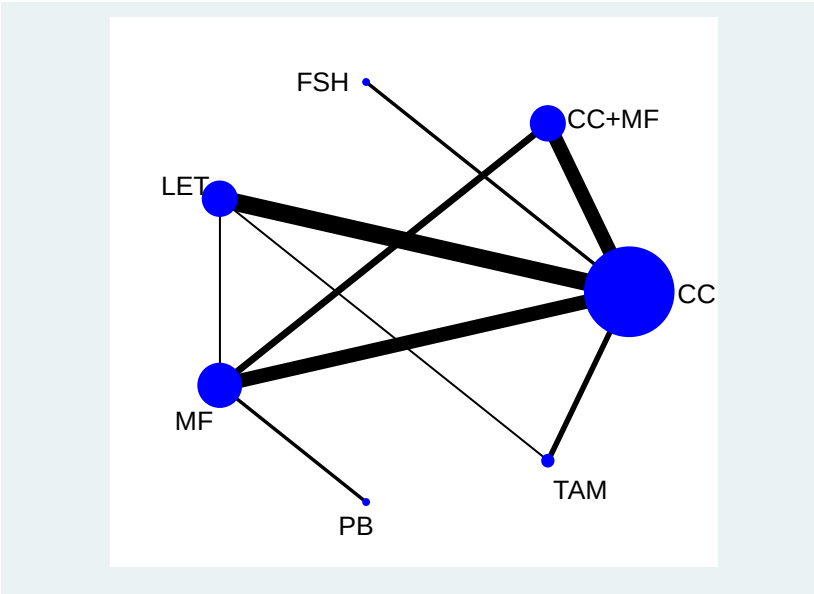
5b. live birth



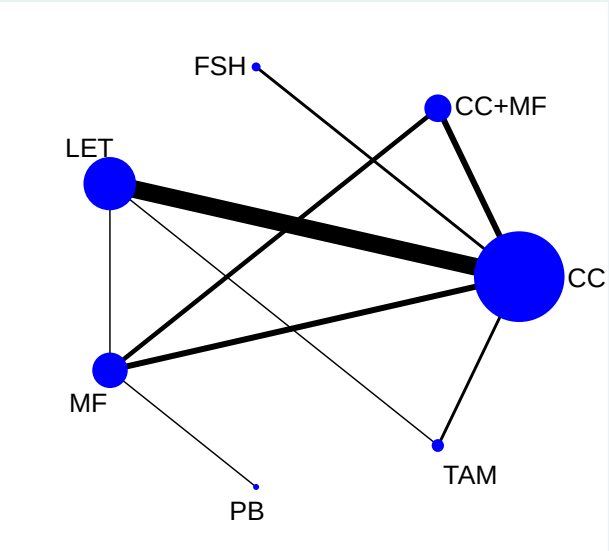
5c. ovulation



5d. miscarriage

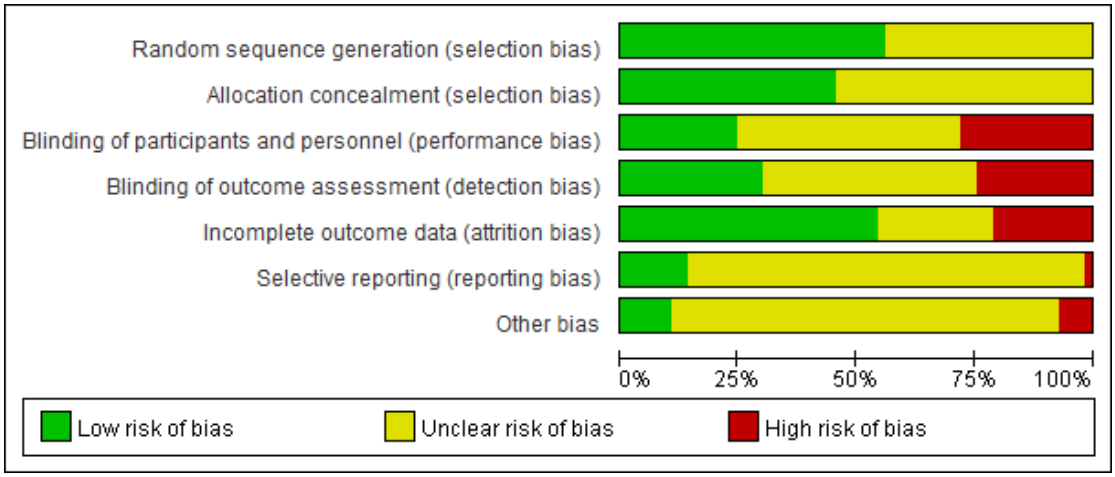


5e. multiple pregnancy

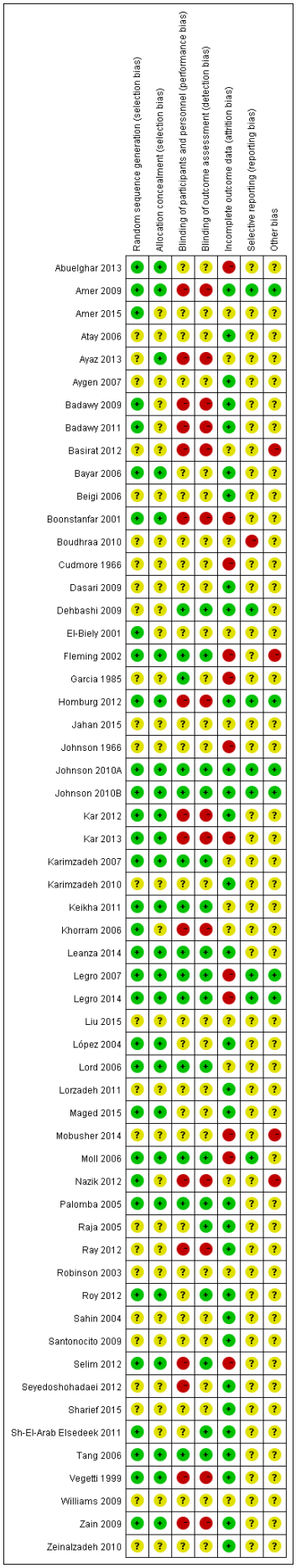


Appendix 6 Risk of bias evaluation.

6a. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.



6b. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Abuelghar 2013
Amer 2009
Amer 2015
Atay 2006
Ayaz 2013
Aygen 2007
Badawy 2009
Badawy 2011
Basirat 2012
Bayar 2006
Beigi 2006
Boonstanfar 2001
Boudhraa 2010
Cudmore 1966
Dasari 2009
Dehbashi 2009
El-Biely 2001
Fleming 2002
Garcia 1985
Homburg 2012
Jahan 2015
Johnson 1966
Johnson 2010A
Johnson 2010B
Kar 2012
Kar 2013
Karimzadeh 2007
Karimzadeh 2010
Kelkha 2011
Khorram 2006
Leanza 2014
Legro 2007
Legro 2014
Liu 2015
López 2004
Lord 2006
Lorzadeh 2011
Maged 2015
Mobusher 2014
Moll 2006
Nazik 2012
Palomba 2005
Raja 2005
Ray 2012
Robinson 2003
Roy 2012
Sahin 2004
Santonocito 2009
Selim 2012
Seyedoshohadaei 2012
Sharief 2015
Sh-El-Arab Elsedeek 2011
Tang 2006
Vegetti 1999
Williams 2009
Zain 2009
Zeinalzadeh 2010

Appendix 7 Pairwise meta-analysis results for direct comparisons of interventions

Comparisons		**Pairwise meta-analysis odds ratio (95% CI)**	**No. of trials**	**No. of participants**	**Heterogeneity I^2**
Pregnancy					
PB	vs CC	0.20(0.05-0.74)	3	136	0%
LET		1.53(1.26-1.85)	21	3553	24.3%
MF		1.10(0.62-1.95)	9	1335	73.1%
CC+MF		1.56(1.24-1.97)	19	2070	12.2%
TAM		0.64(0.36-1.12)	4	661	43.7%
FSH		1.57(1.04-2.37)	2	378	0%
LOD		0.52(0.19-1.44)	1	72	N/A
MF	vs PB	3.58(2.06-6.21)	5	494	0%
MF	vs LET	0.73(0.41-1.32)	1	304	N/A
TAM		0.67(0.30-1.47)	1	100	N/A
CC+MF	vs MF	1.92(0.90-4.06)	5	818	71.8%
Live birth					
LET	vs CC	1.60(1.30-1.98)	9	1990	0%
MF		1.00(0.45-2.22)	8	1155	80.9%
CC+MF		1.14(0.81-1.61)	7	950	12.4%
TAM		0.96(0.26-3.55)	2	195	35.3%
FSH		1.50(0.98-2.29)	2	378	0%
MF	vs PB	2.87(0.51-16.02)	1	65	N/A
MF	vs LET	0.38(0.19-0.78)	1	304	N/A
TAM		0.71(0.32-1.60)	1	100	N/A
CC+MF	vs MF	2.48(1.24-4.95)	4	640	51.1%
Ovulation (per woman randomised)					
PB	vs CC	0.15(0.07-0.34)	3	136	0%
LET		1.89(1.55-2.30)	14	2568	8.8%
MF		0.62(0.32-1.22)	7	1119	82.9%
CC+MF		1.46(1.01-2.12)	14	1407	54.5%
TAM		0.61(0.43-0.86)	3	566	0%
FSH		3.11(0.76-12.79)	1	76	N/A
LOD		0.70(0.27-1.83)	1	72	N/A
MF	vs PB	3.63(0.45-29.35)	3	309	92.9%
MF	vs LET	0.14(0.09-0.24)	1	304	N/A
TAM		0.75(0.31-1.78)	1	100	N/A
CC+MF	vs MF	3.20(1.85-5.52)	4	640	44.4%
Multiple pregnancy (per woman randomised)					
LET	vs CC	0.45(0.22-0.91)	12	2460	0%
MF		0.22(0.05-0.96)	4	976	0%
CC+MF		0.57(0.19-1.74)	4	892	0%
TAM		0.48(0.06-3.76)	2	471	0%

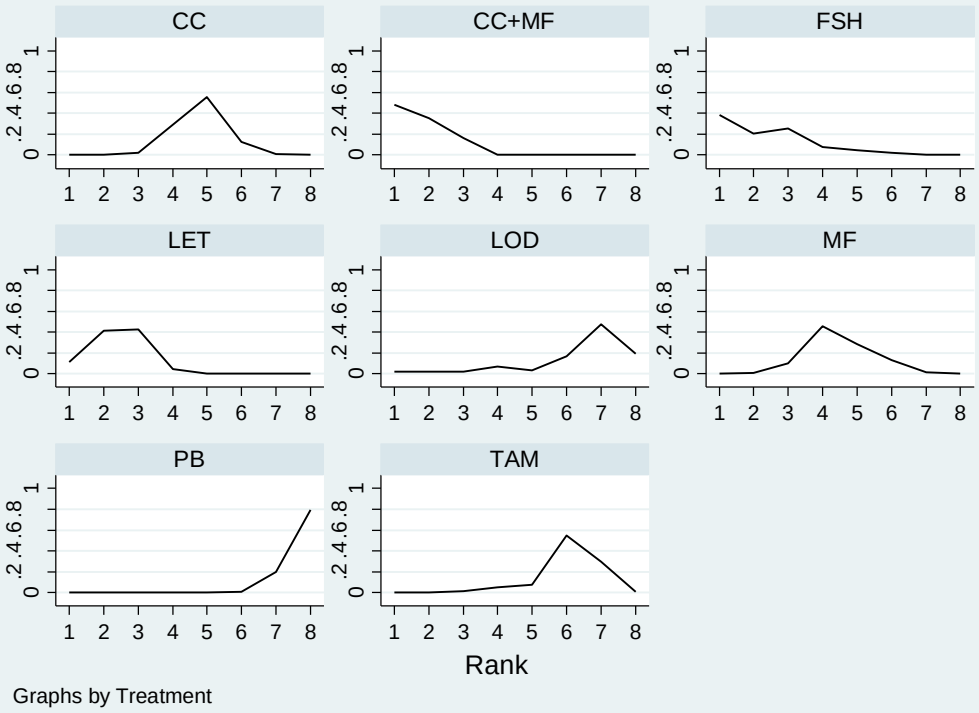
FSH		3.62(0.58-22.80)	2	378	0%
MF	vs PB	0.33(0.01-8.49)	1	65	N/A
MF	vs LET	0.20(0.01-4.15)	1	304	N/A
TAM		3.06(0.12-76.95)	1	100	N/A
CC+MF	vs MF	2.36(0.42-12.39)	4	665	0%
Miscarriage (per woman randomised)					
LET	vs CC	1.00(0.62-1.62)	10	2302	10.6%
MF		0.76(0.32-1.82)	8	1155	29.1%
CC+MF		1.38(0.85-2.24)	8	991	0%
TAM		0.56(0.19-1.68)	3	566	23.4%
FSH		1.44(0.57-3.63)	2	378	0%
MF	vs PB	1.02(0.28-3.73)	2	265	0%
MF	vs LET	0.33(0.13-8.20)	1	304	N/A
TAM		0.73(0.16-3.46)	1	100	N/A
CC+MF	vs MF	1.37(0.66-2.87)	4	640	10.9%
Miscarriage (per pregnant woman)					
LET	vs CC	0.79(0.52-1.21)	10	718	0%
MF		0.70(0.19-2.63)	8	277	54.9%
CC+MF		1.35(0.74-2.46)	8	384	0%
TAM		0.83(0.31-2.19)	3	123	0%
FSH		0.99(0.37-2.67)	2	164	0%
MF	vs PB	0.28(0.06-1.19)	2	63	0%
MF	vs LET	0.41(0.02-10.64)	1	55	N/A
TAM		0.93(0.18-4.72)	1	45	N/A
CC+MF	vs MF	0.67(0.27-1.66)	4	174	0%

(Abbreviations: CC, clomiphene citrate; PB, placebo or no treatment; LET, letrozole; MF, metformin; TAM, tamoxifen; FSH, follicle stimulating hormone; LOD, laparoscopic ovarian drilling)

An odds ratios < 1 favour the second intervention and an odds ratios > 1 favour the first intervention.

Appendix 8 Ranking of treatments for pregnancy

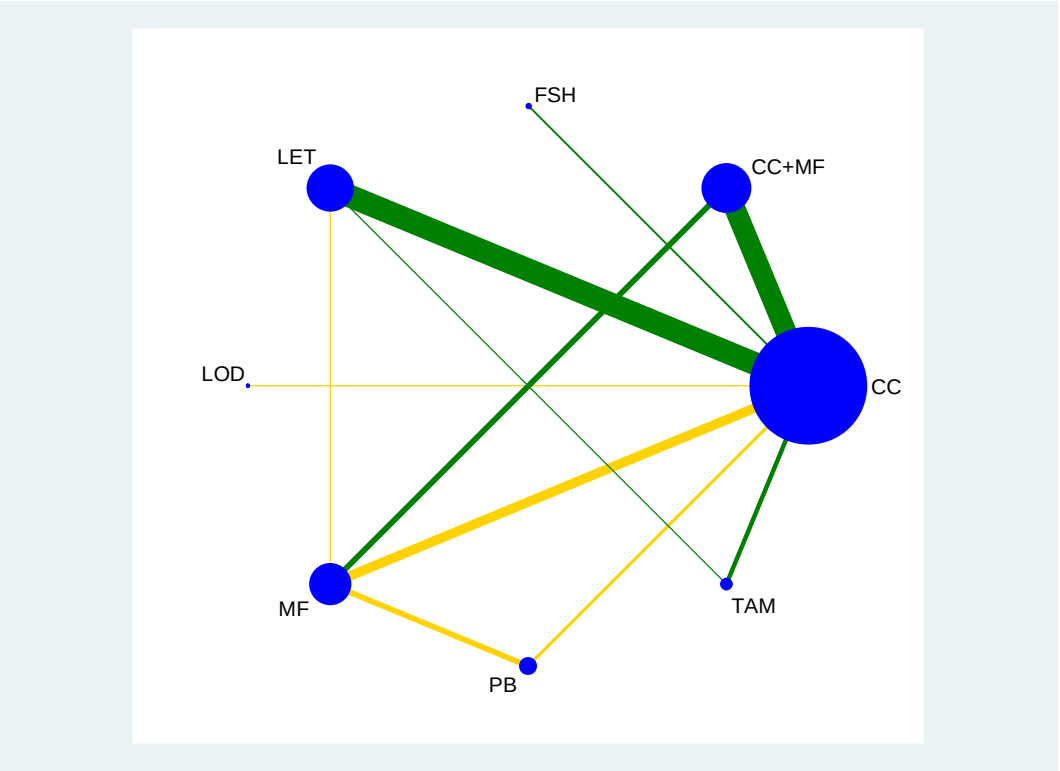
Rankograms below illustrate the probability per rank for each treatment in terms of pregnancy. E.g. for CC, the probabilities of being the best treatment, the second best, to the worst (eighth) are 0%, 0%, 2.4%, 29.0%, 55.5%, 12.3%, 0.8% and 0%, respectively.



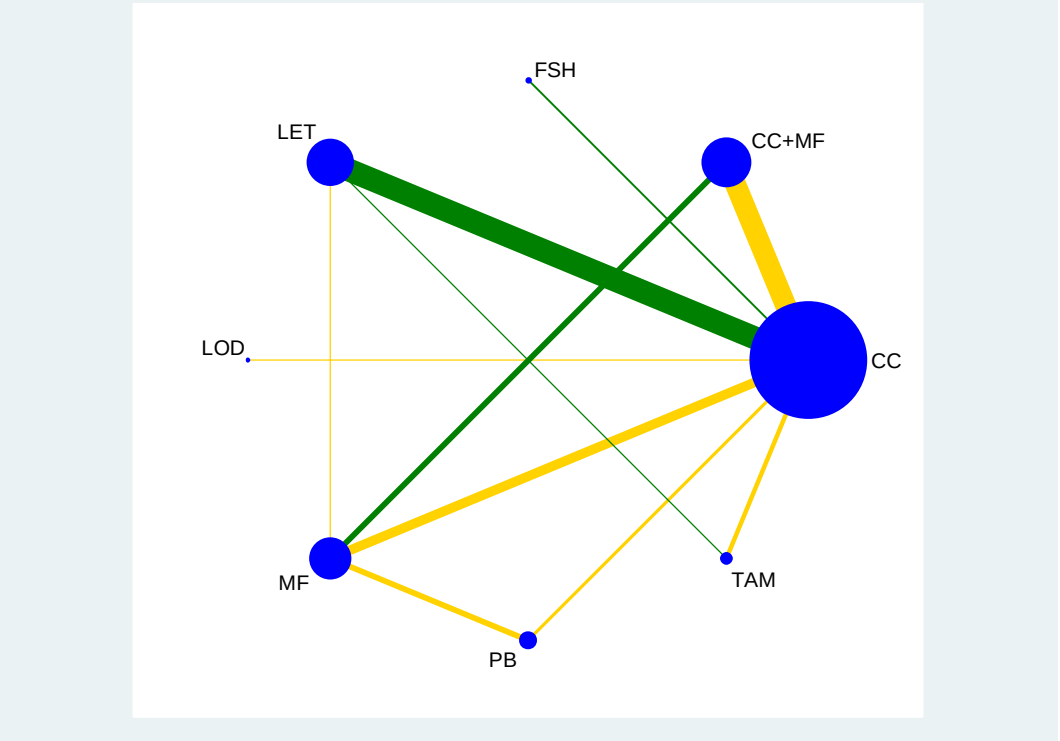
Appendix 9 Network plot for pregnancy incorporating risk of bias assessment

9a. Risk of bias in randomisation

Coloured edges are based on adequacy of randomisation in the majority of the trials in each comparison. Green, yellow and red colours represent low, unclear and high risk, respectively.

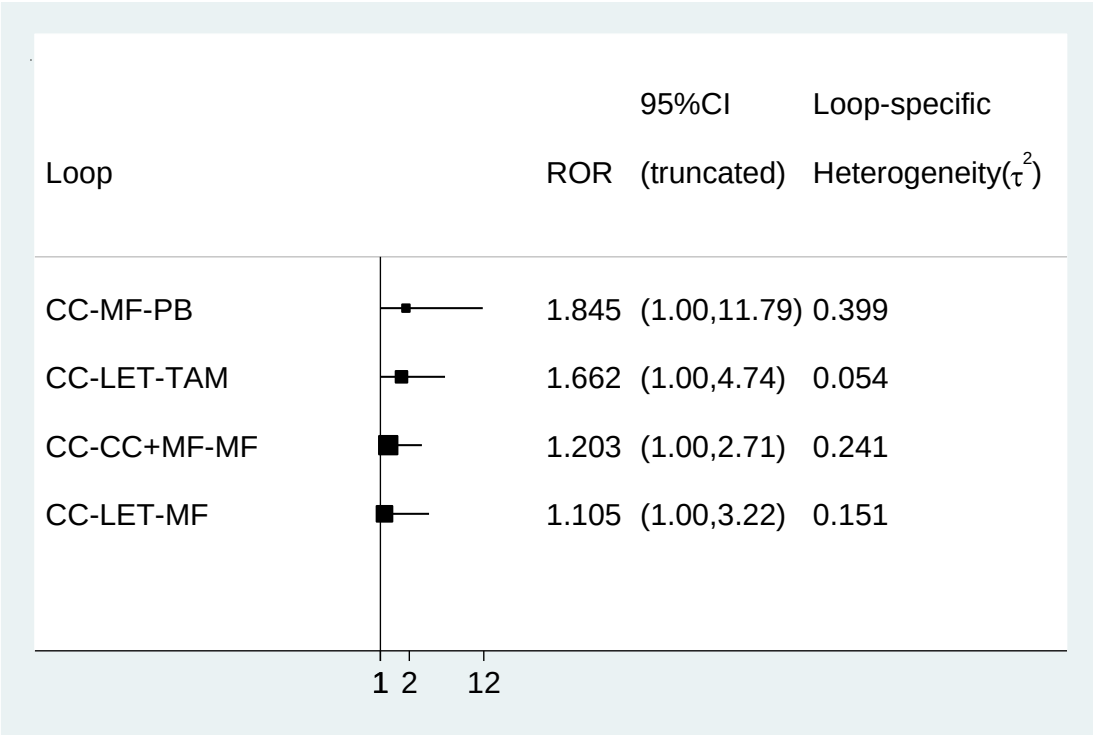


9b. Risk of randomisation in allocation concealment



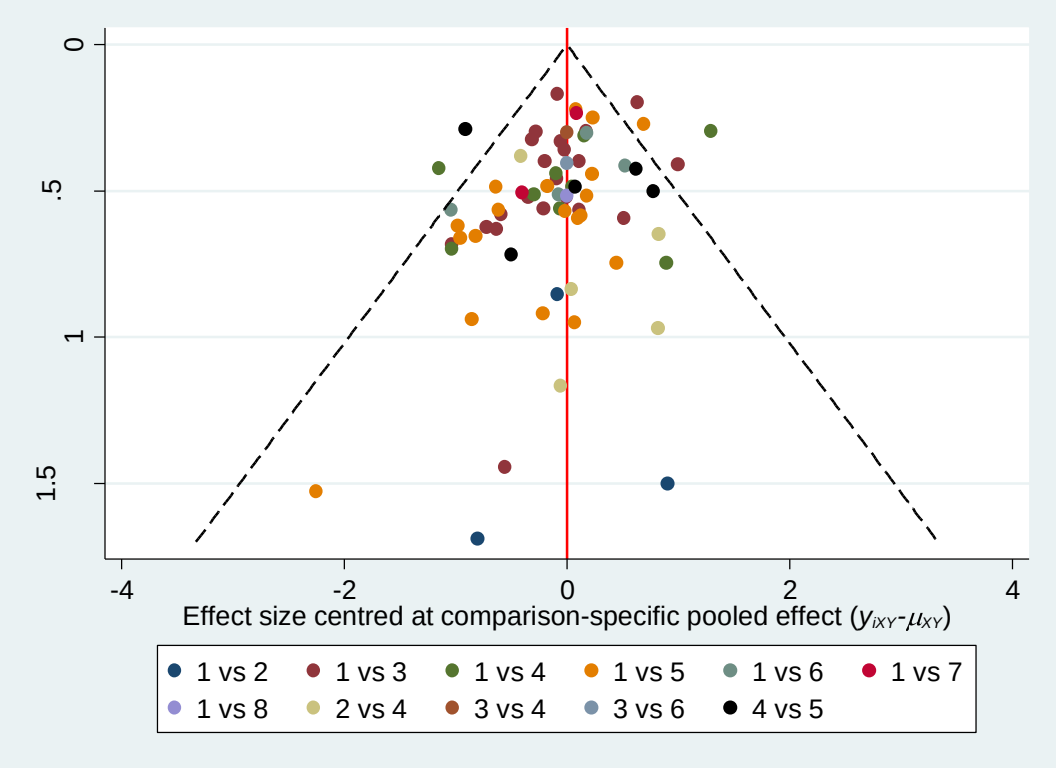
Appendix 10 Inconsistency plot for pregnancy

We estimated inconsistency as the logarithm of the ratio of two odds ratios (RoR) from direct and indirect evidence in the loop (also named inconsistency factor IF) and the corresponding 95% CI for each IF in each closed triangular or quadratic loop. RoR values is close to 1 mean that the two sources are in agreement. The inconsistency plot shows that in a total of 4 loops there is none with statistically significant inconsistency as all confidence intervals for RORs are compatible with zero inconsistency (RoR= 1).



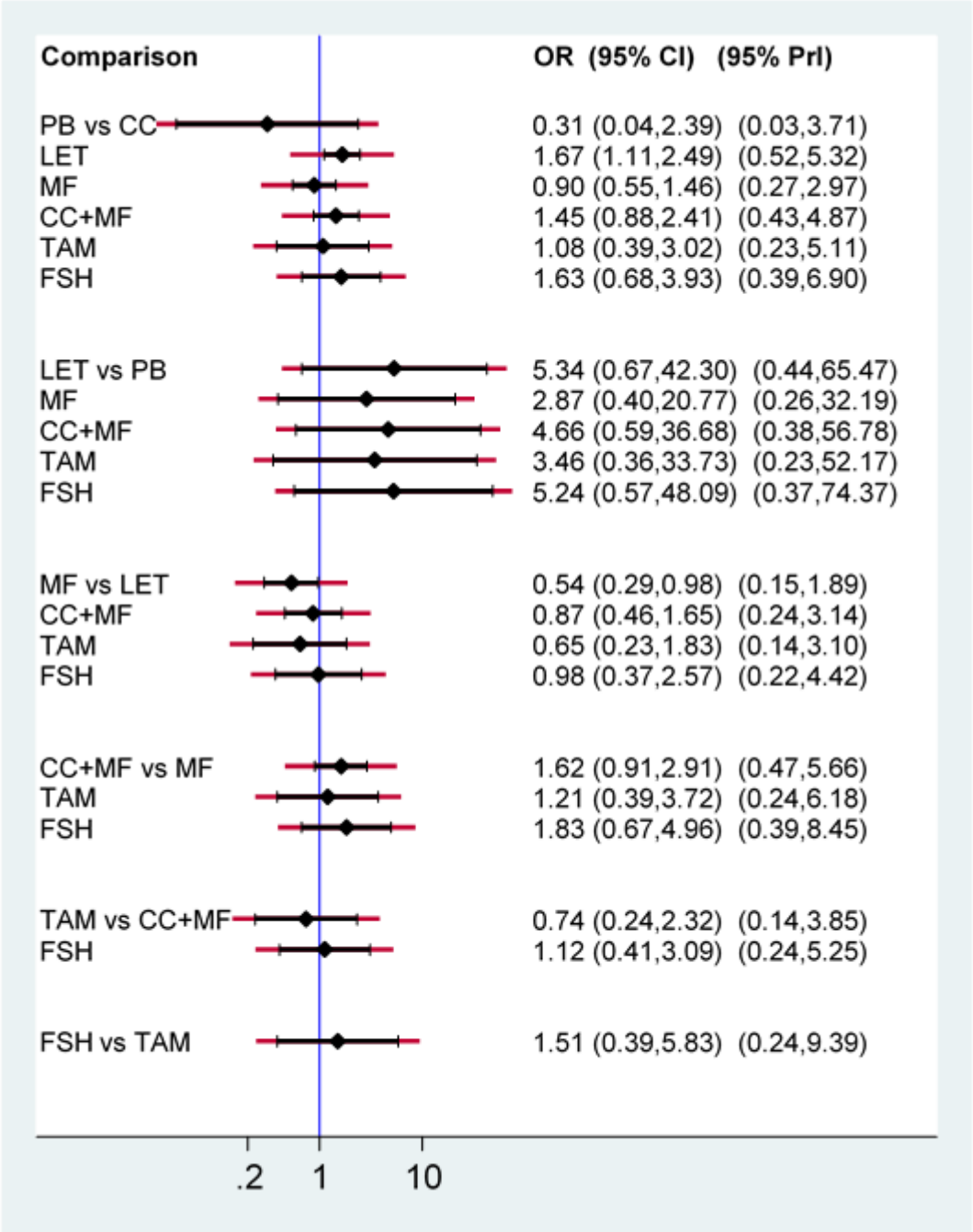
Appendix 11 Comparison-adjusted funnel plot for pregnancy

The red line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. Different colors correspond to different comparisons. (1-clomiphene; 2-placebo/no treatment; 3-letrozole; 4-metformin; 5-clomiphene plus metformin; 6-tamoxifen; 7-FSH; 8-LOD)

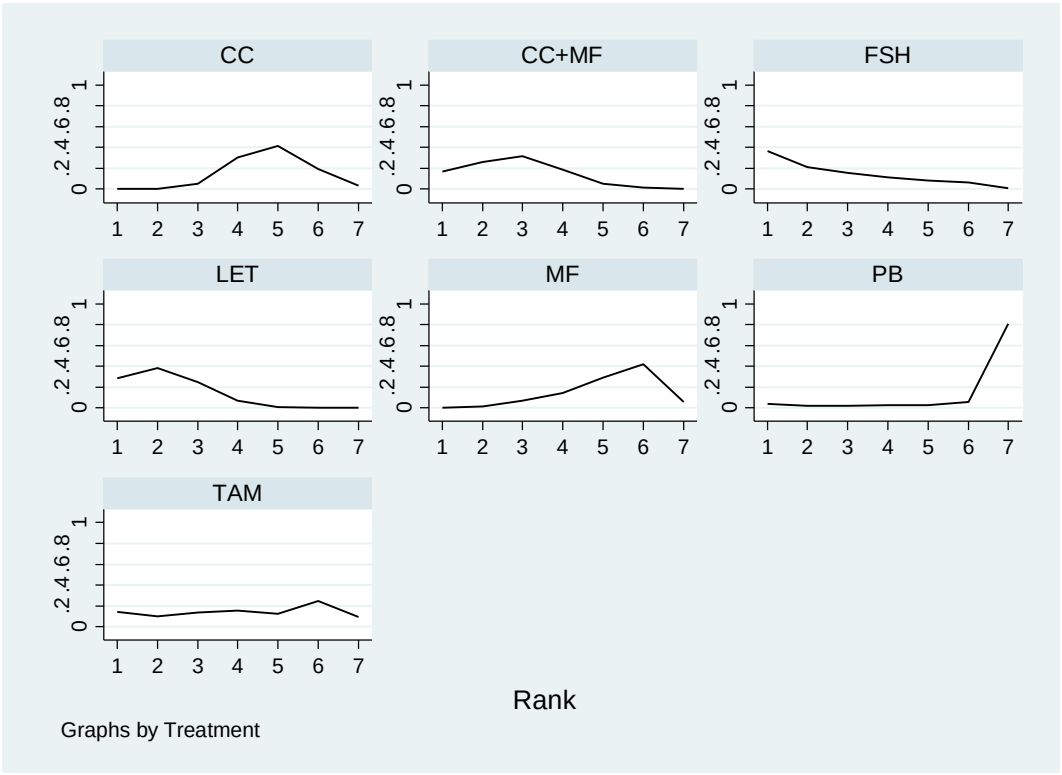


Appendix 12 Network meta-analysis results for live birth

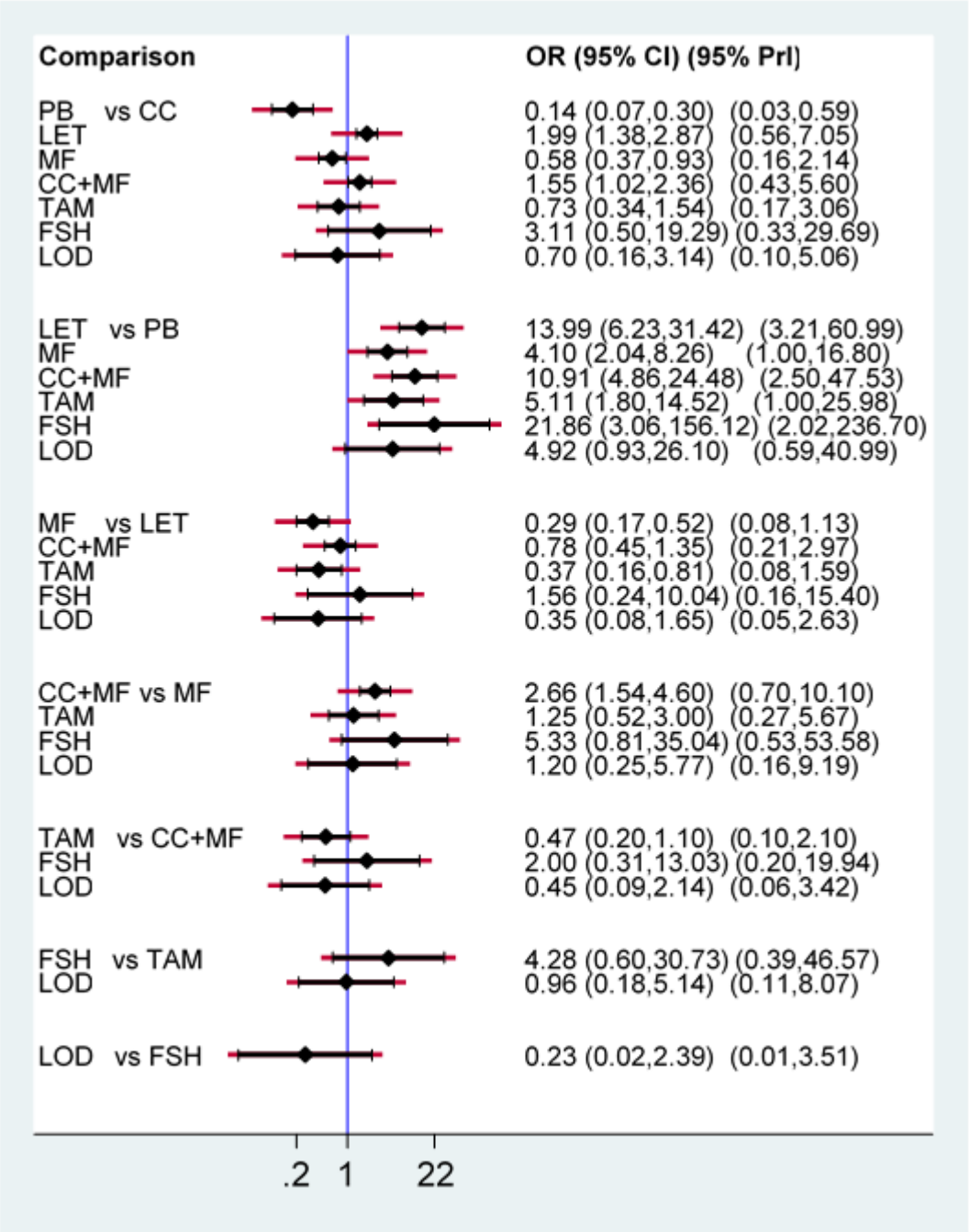
The diamond in each line represents the estimate summary odds ratios of each comparison. The black lines represent the confidence intervals for summary odds ratios for each comparison and the red lines (overall length of the lines) the respective predictive intervals. The blue line is the line of no effect (odds ratio equal to 1). An odds ratio >1 favours the first intervention and an odds ratio < 1 favours the second. (Abbreviations: OR, odds ratio; CI, confidence interval; PrI, predictive interval; CC, clomiphene citrate; PB, placebo or no treatment; LET, letrozole; MF, metformin; TAM, tamoxifen; FSH, follicle stimulating hormone; LOD, laparoscopic ovarian drilling)



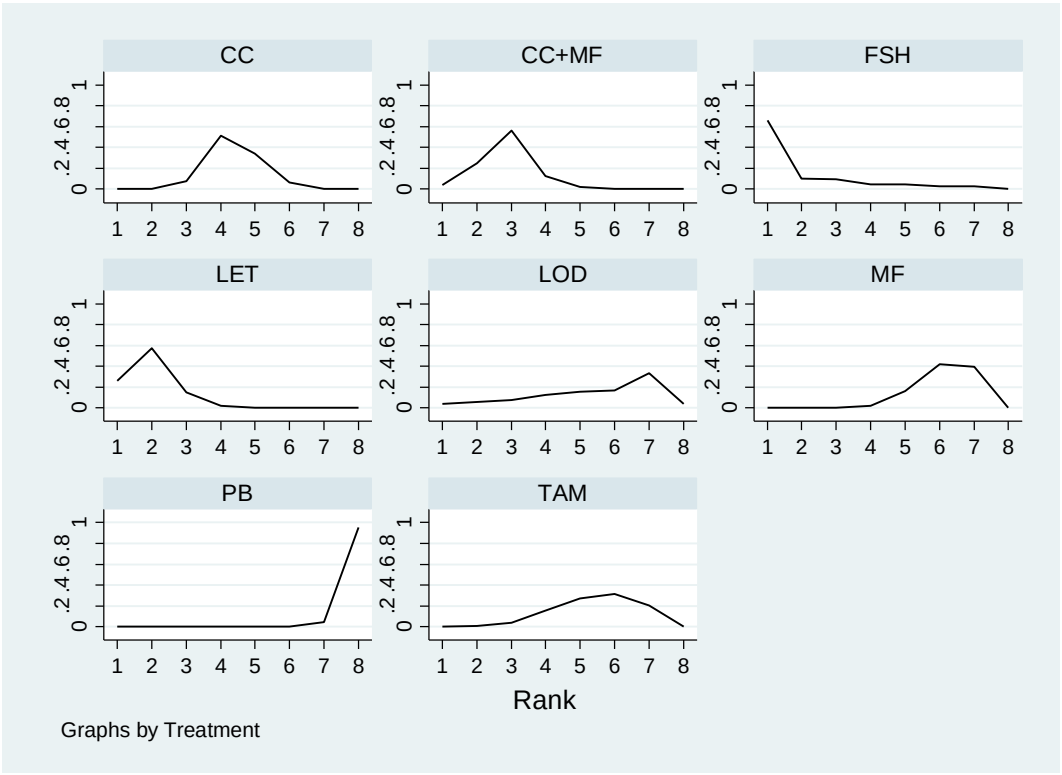
Appendix 13 Ranking of treatments for live birth



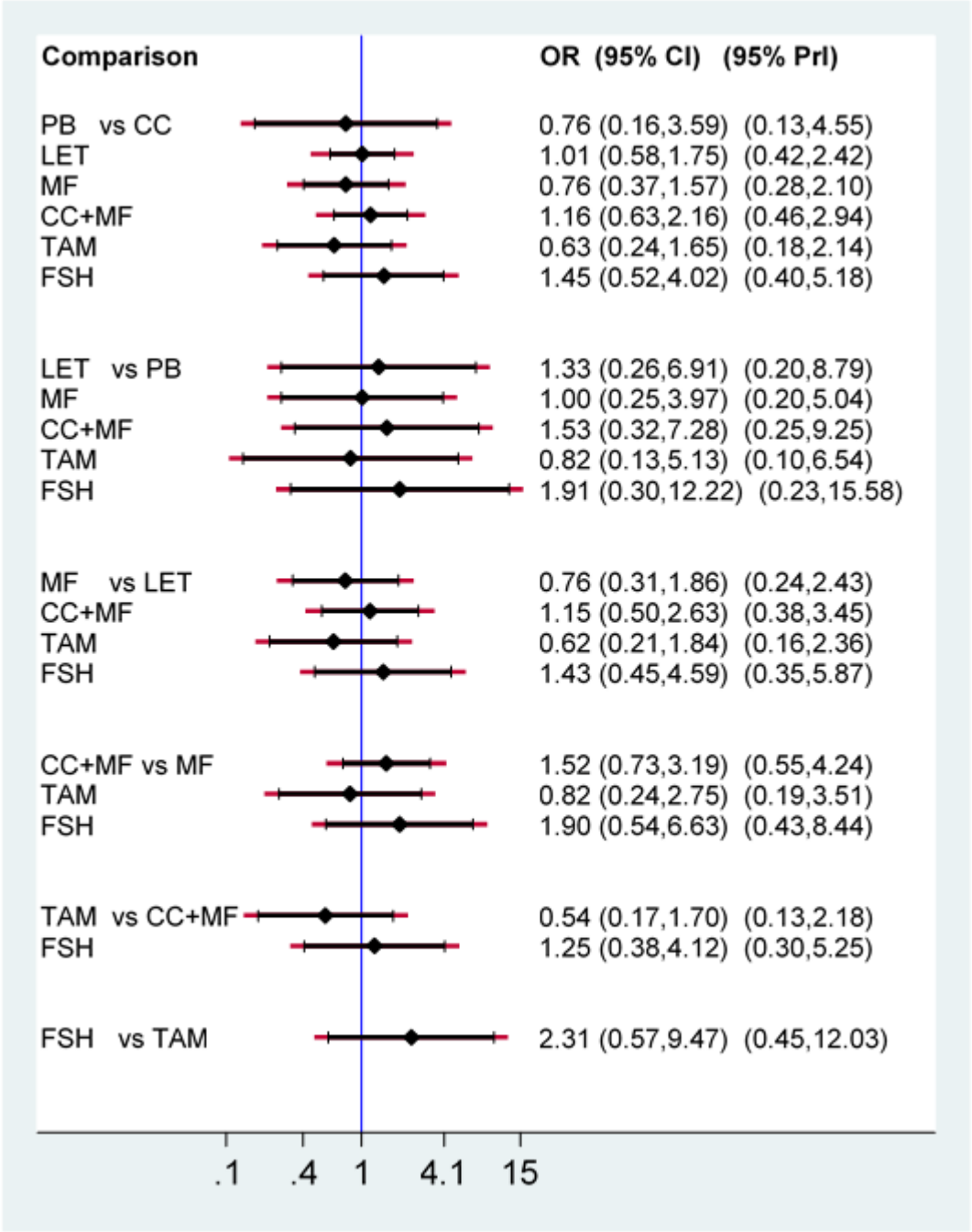
Appendix 14 Network meta-analysis results for ovulation



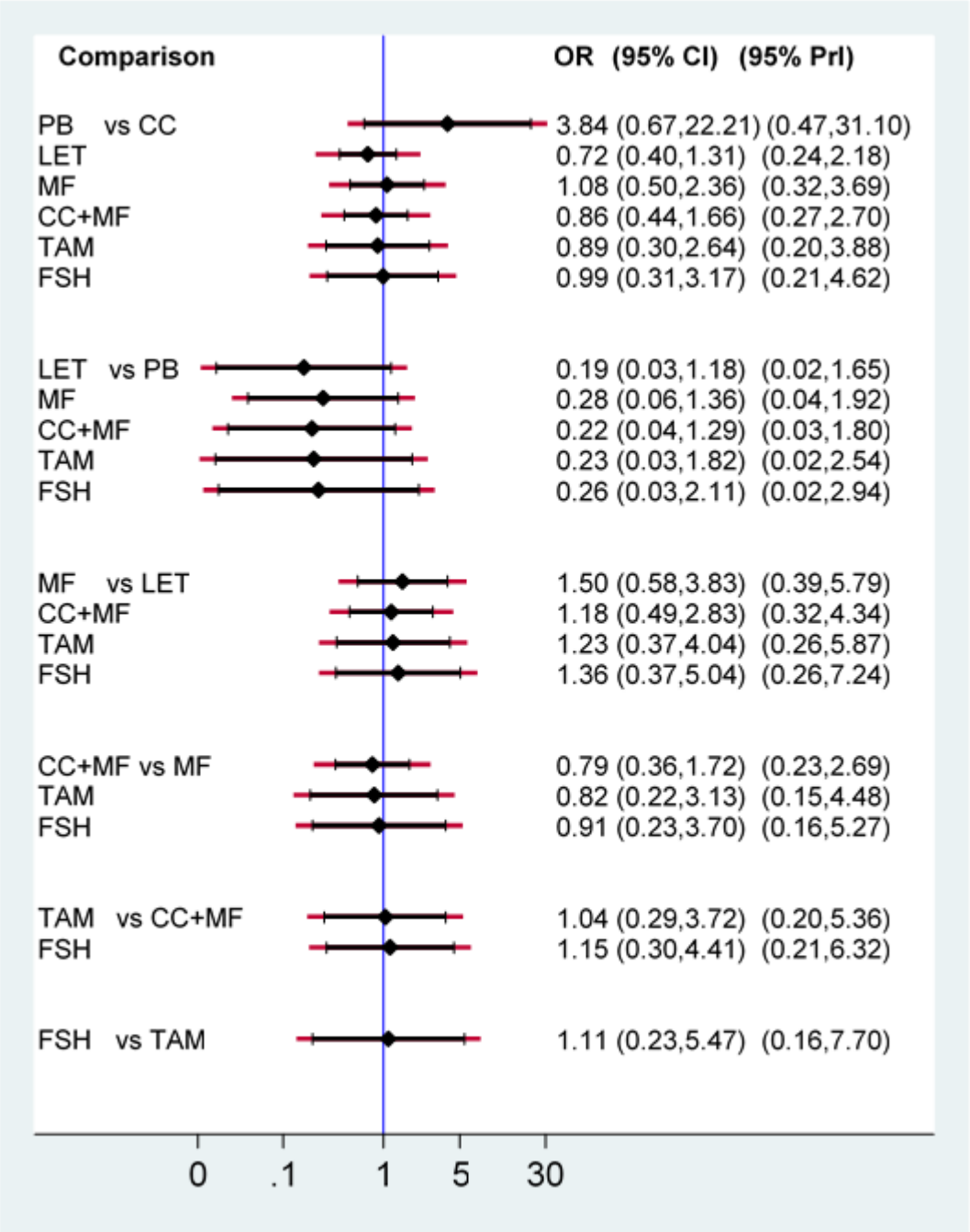
Appendix 15 Ranking of treatments for ovulation



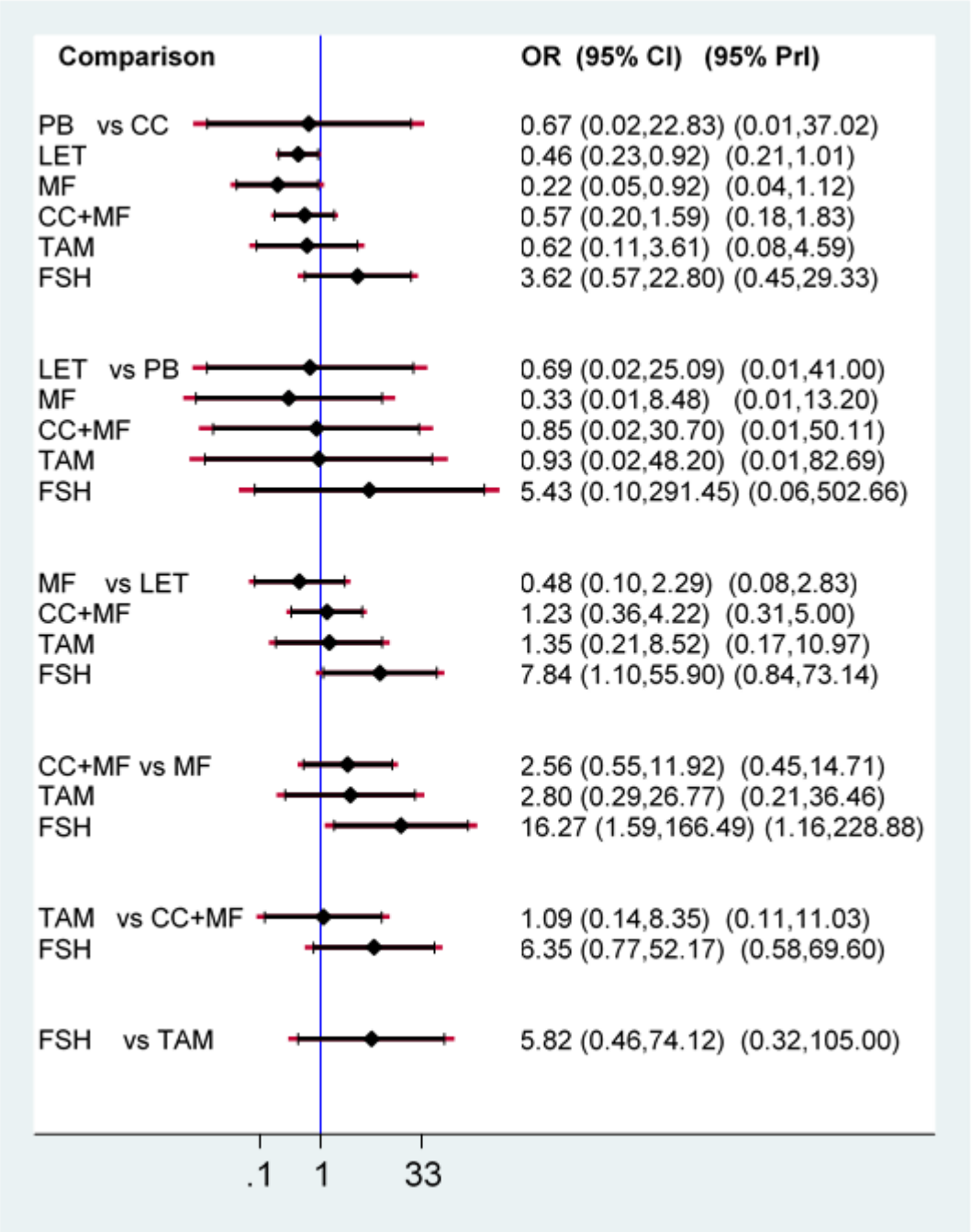
Appendix 16 Network meta-analysis results for miscarriage per woman randomised



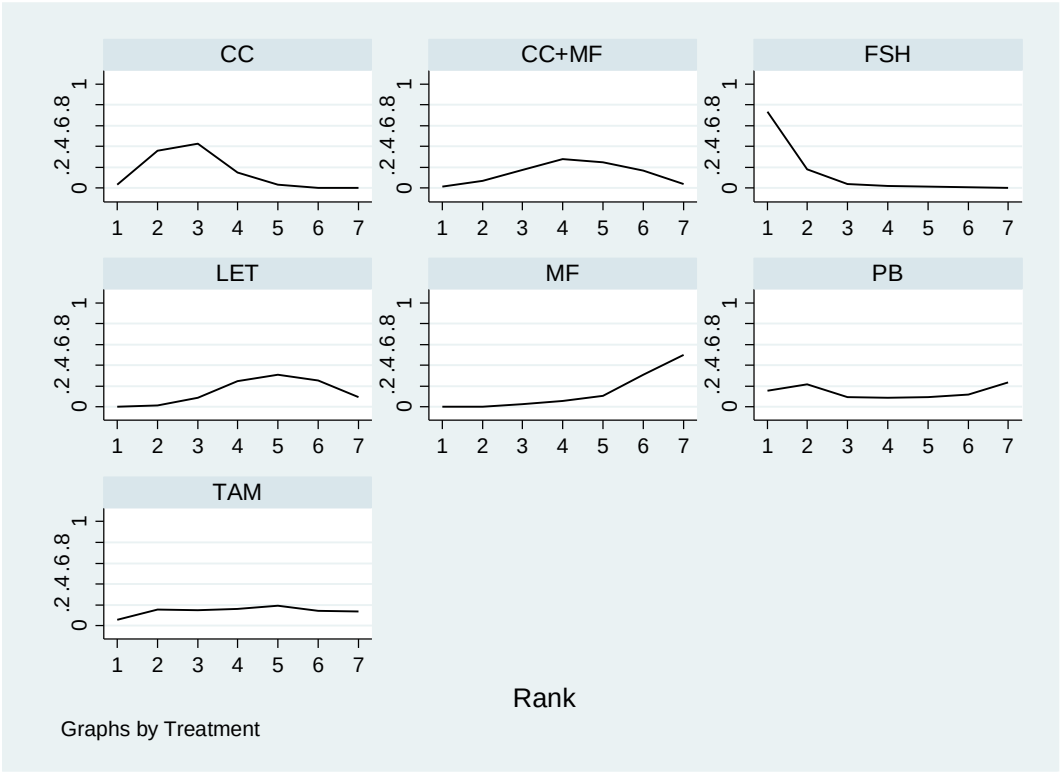
Appendix 17 Network meta-analysis results for miscarriage per pregnancy



Appendix 18 Network meta-analysis results for multiple pregnancy

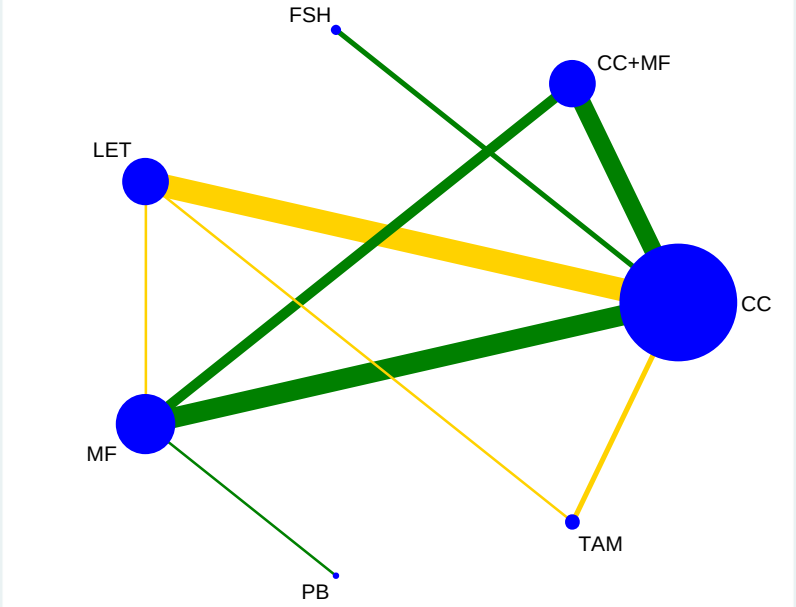


Appendix 19 Ranking of treatments for multiple pregnancy

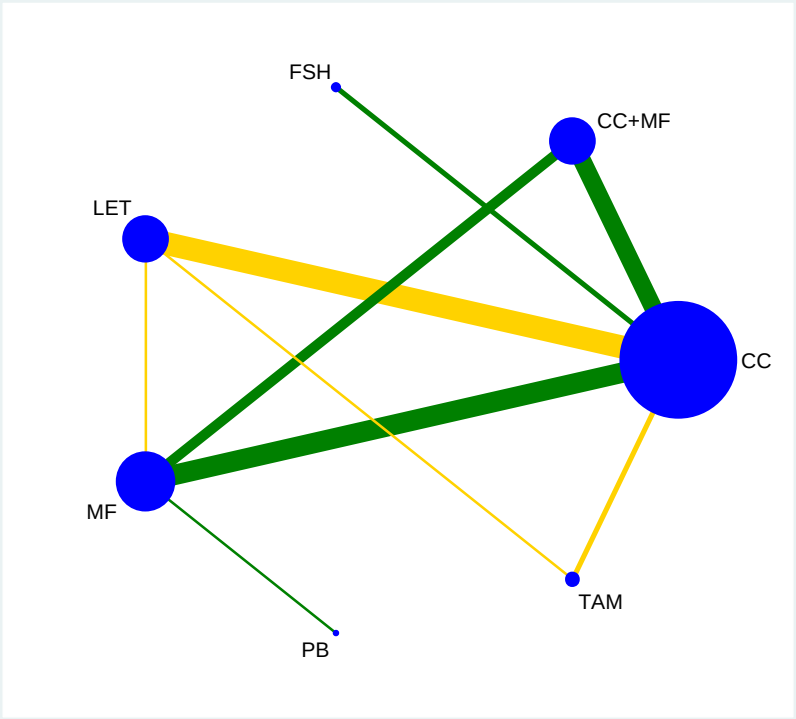


Appendix 20 Network plot for live birth incorporating risk of bias assessment

20a. Risk of bias in randomisation

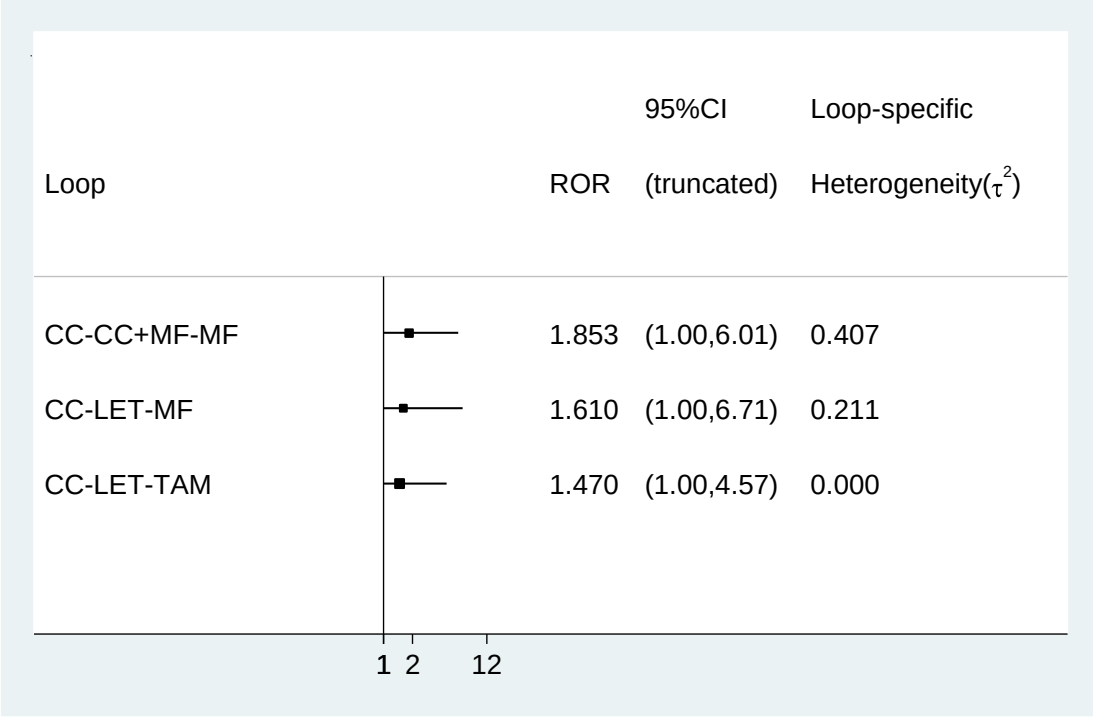


20b. Risk of bias in allocation concealment

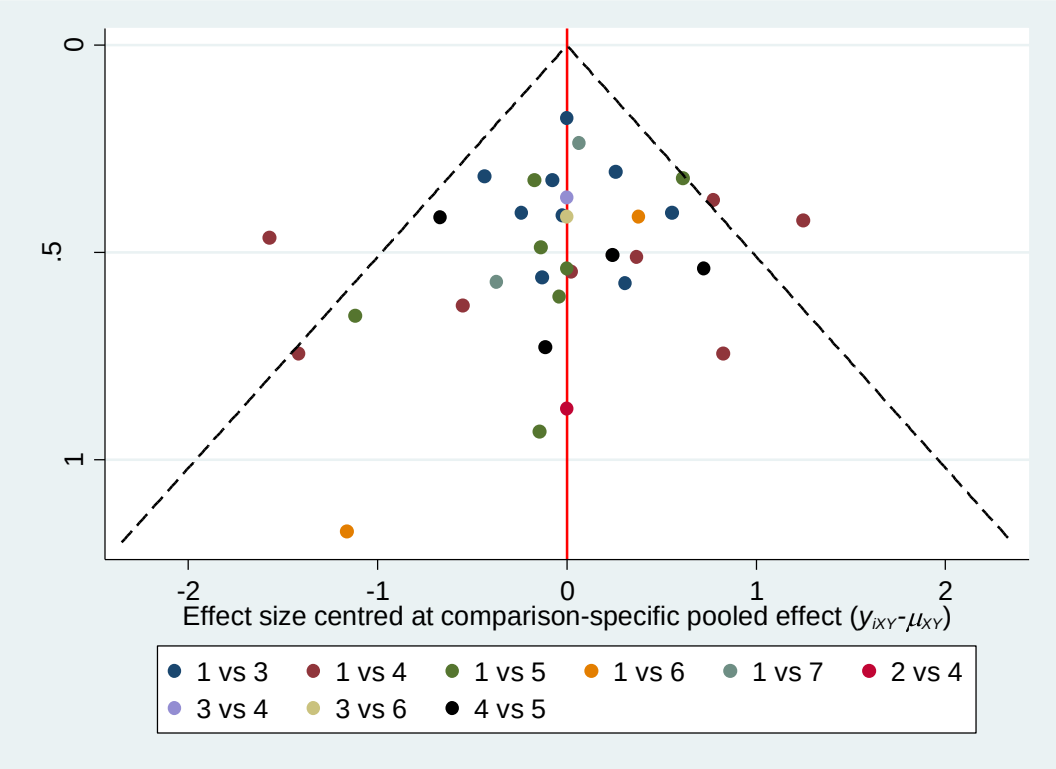


Appendix 21 Inconsistency plot for live birth.

The inconsistency plot shows that in a total of 3 loops there is none with statistically significant inconsistency as all confidence intervals for RORs are compatible with zero inconsistency (RoR= 1).



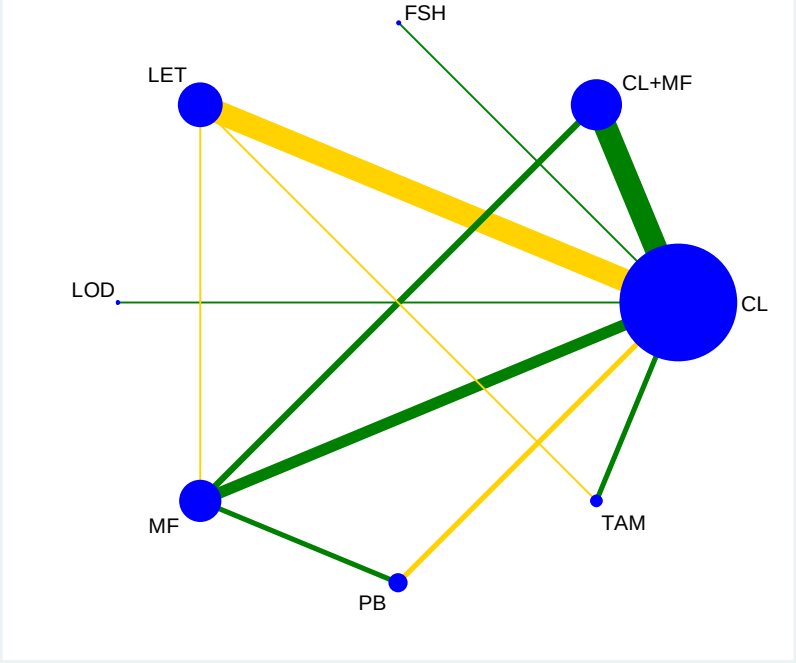
Appendix 22 Comparison-adjusted funnel plot for live birth



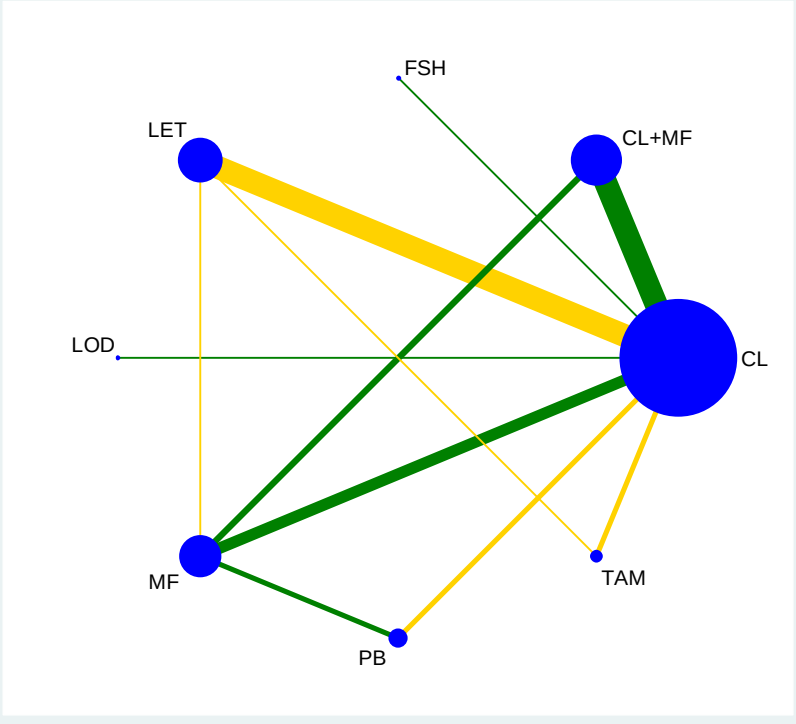
(1-clomiphene; 2-placebo/no treatment; 3-letrozole; 4-metformin; 5-clomiphene plus metformin; 6-tamoxifen; 7-FSH)

Appendix 23 Network plot for ovulation incorporating risk of bias assessment

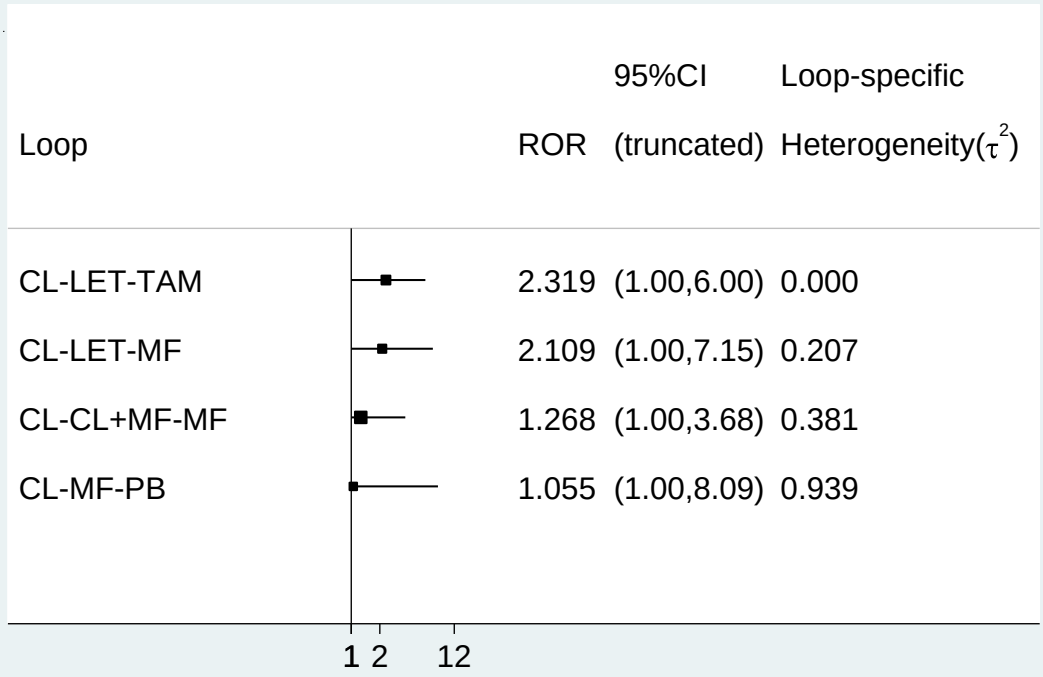
23a. Risk of bias in randomisation



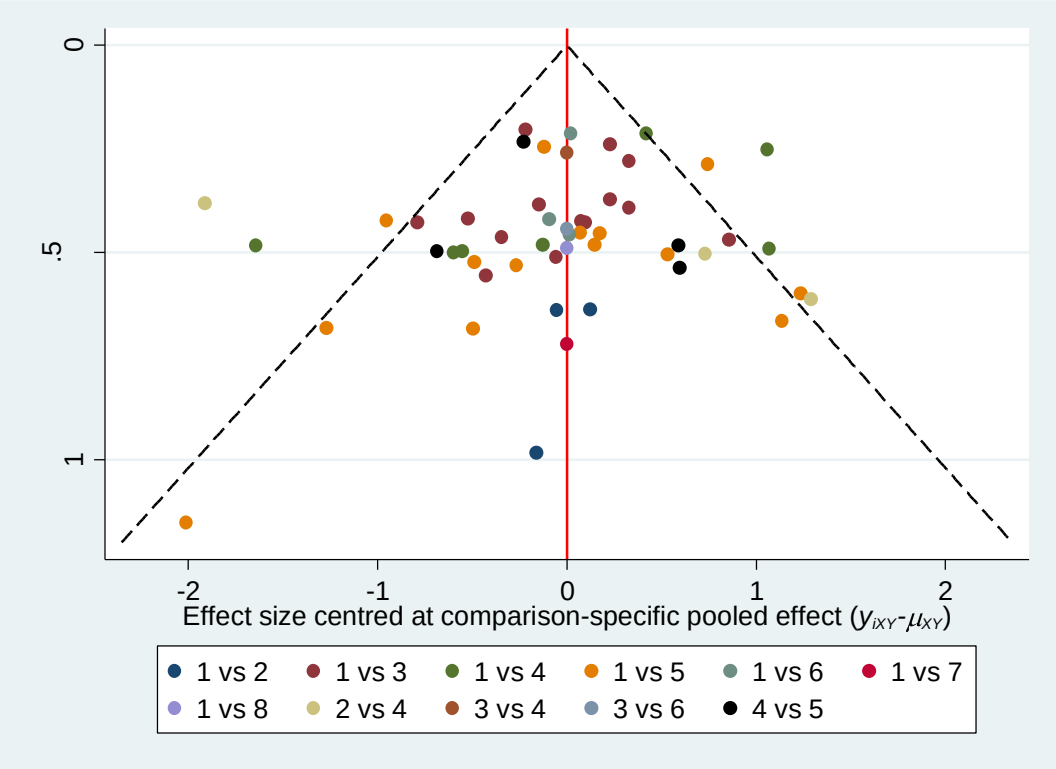
23b.. Risk of bias in allocation concealment



Appendix 24 Inconsistency plot for ovulation



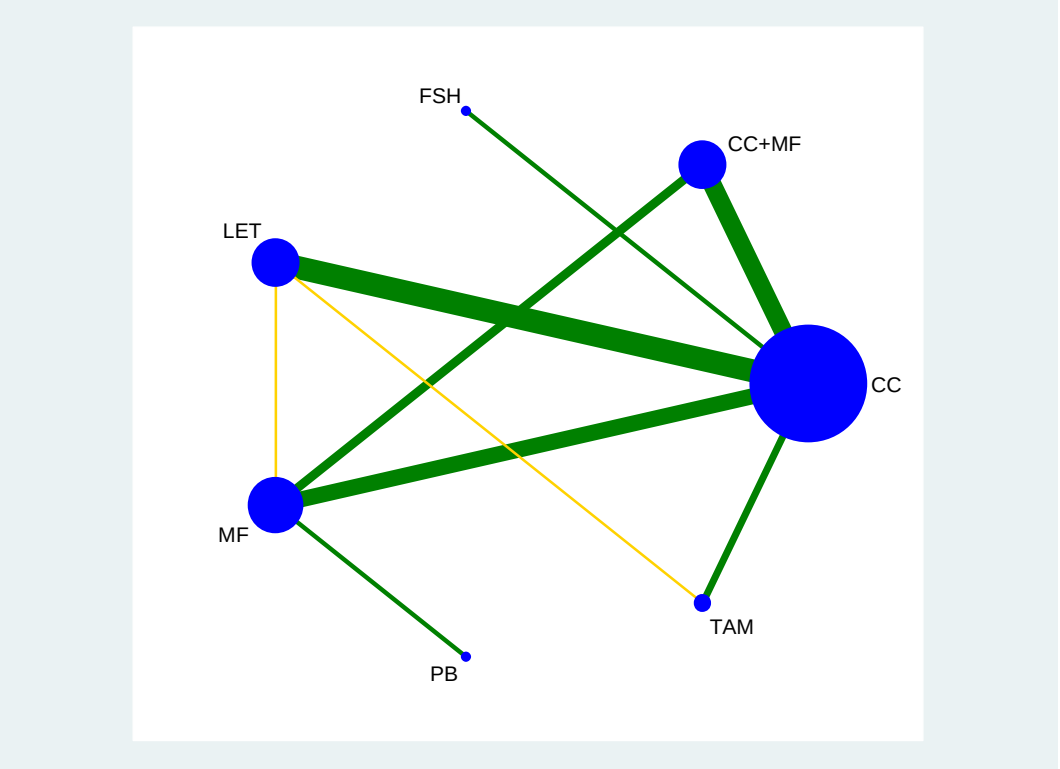
Appendix 25 Comparison-adjusted funnel plot for ovulation



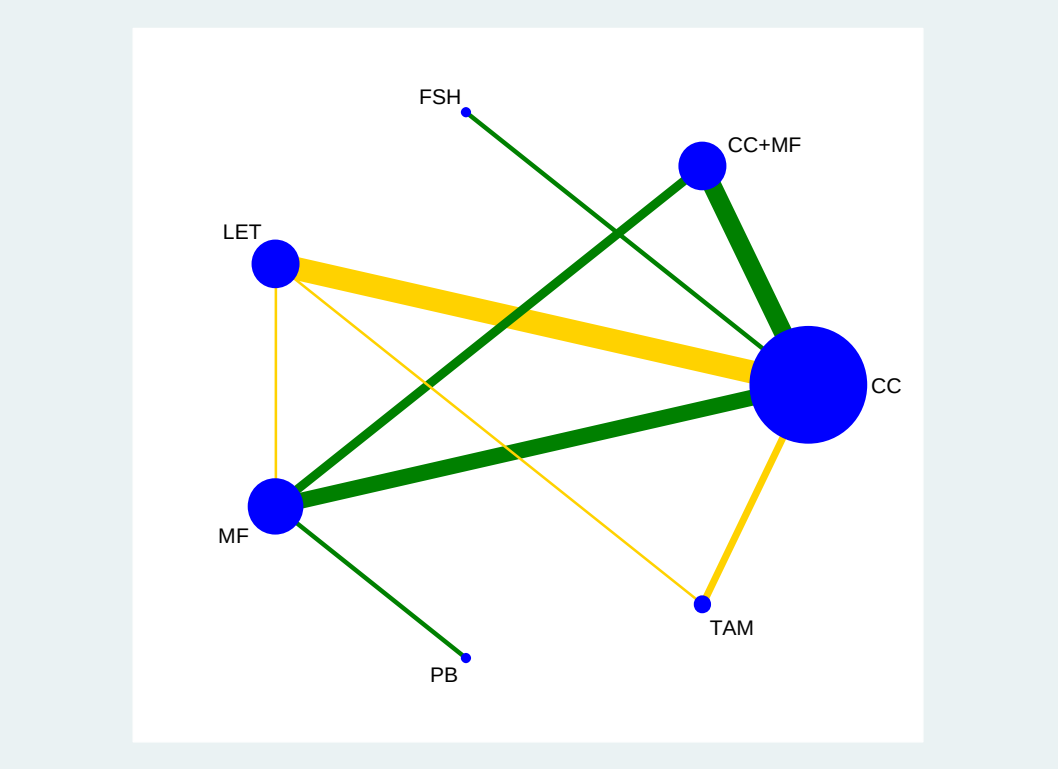
(1-clomiphene; 2-placebo/no treatment; 3-letrozole; 4-metformin; 5-clomiphene plus metformin; 6-tamoxifen; 7-FSH; 8-LOD)

Appendix 26 Network plot for miscarriage incorporating risk of bias assessment

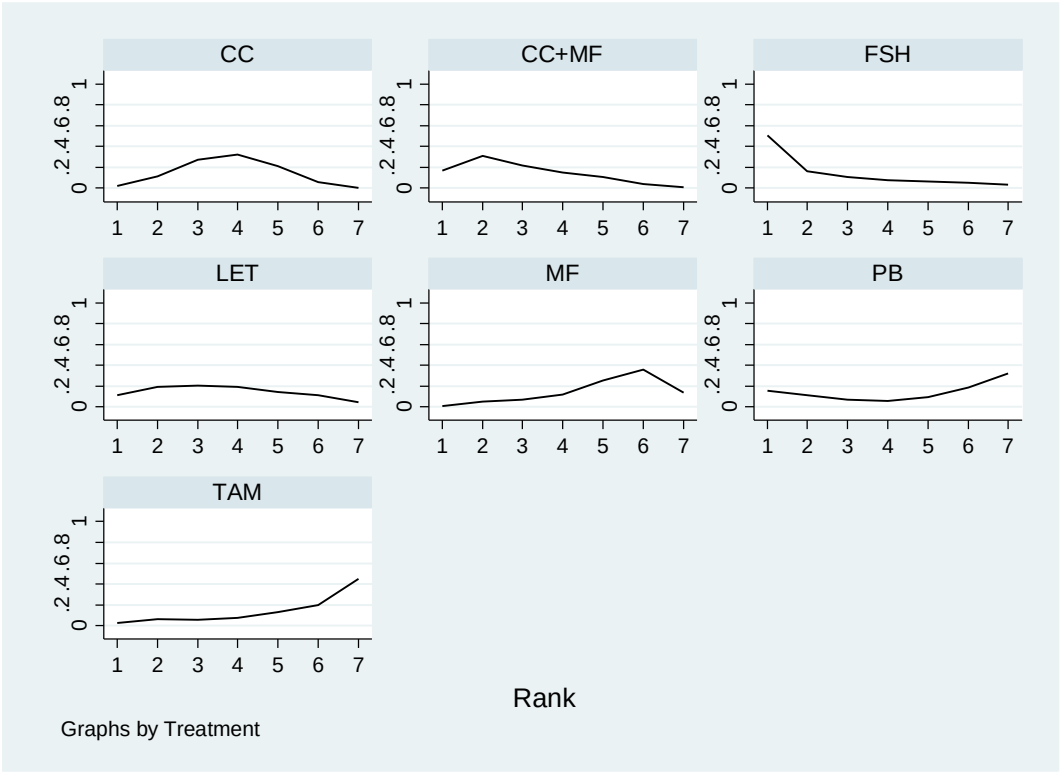
26a. Risk of bias in randomisation



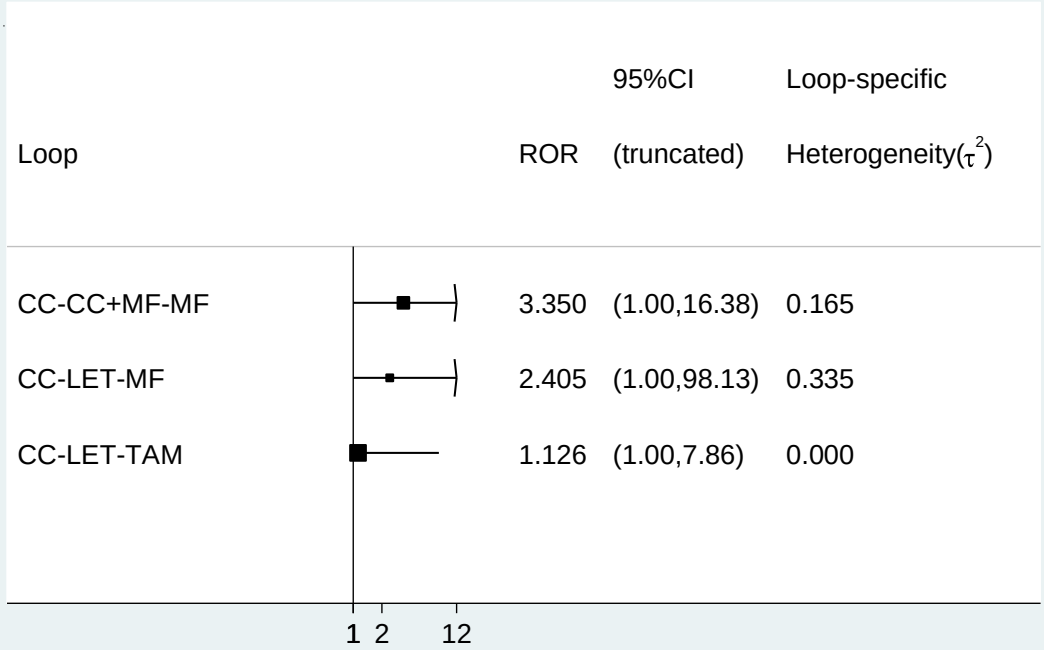
26b. Risk of bias in allocation concealment



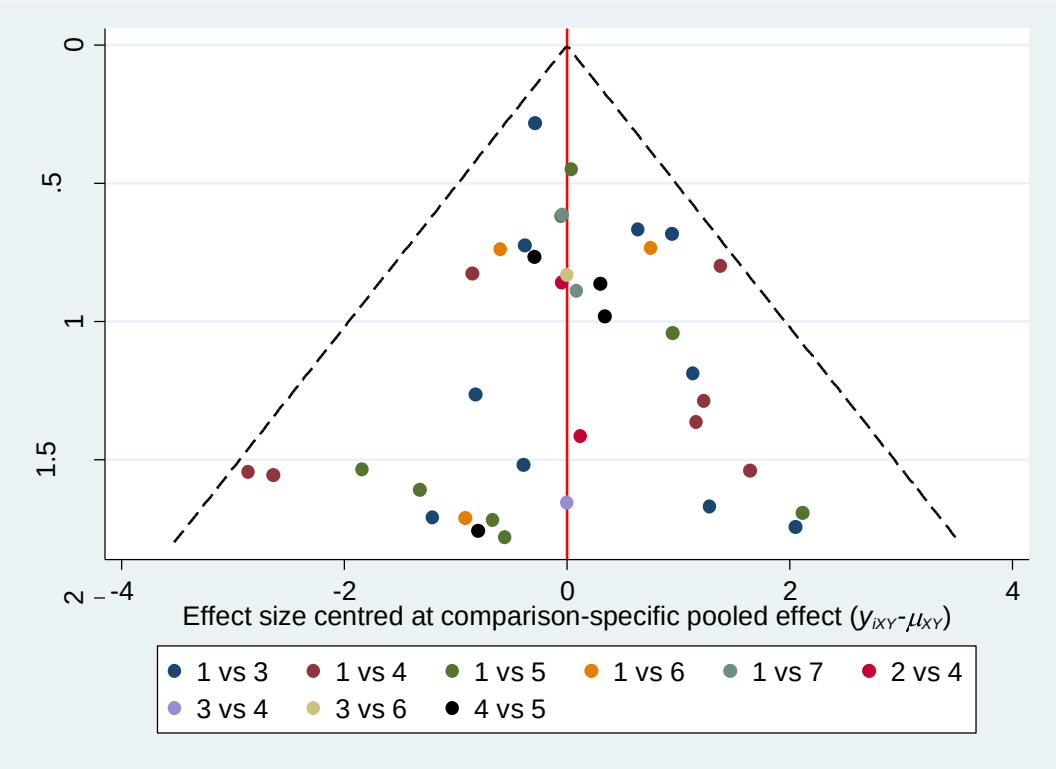
Appendix 27 Ranking of treatments for miscarriage per pregnancy



Appendix 28 Inconsistency plot for miscarriage per pregnancy



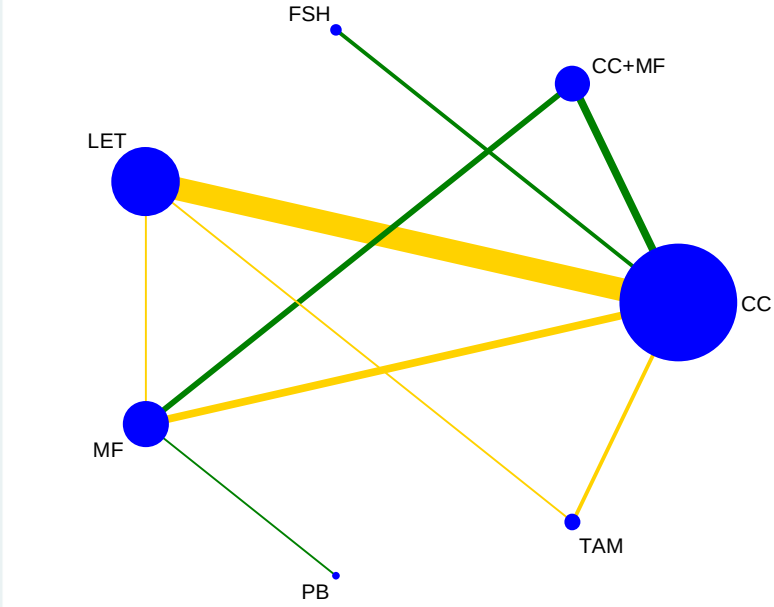
Appendix 29 Comparison-adjusted funnel plot for miscarriage per pregnancy



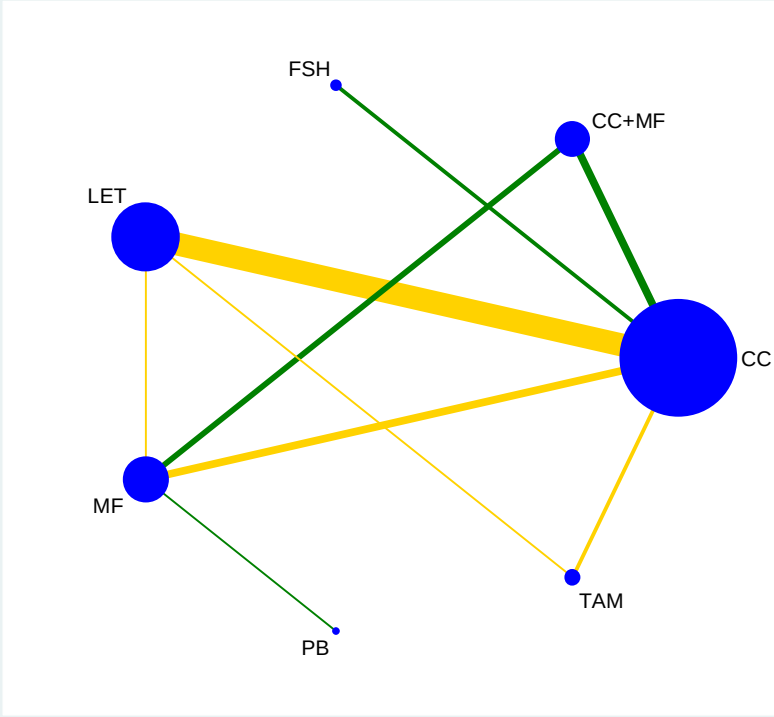
(1-clomiphene; 2-placebo/no treatment; 3-letrozole; 4-metformin; 5-clomiphene plus metformin; 6-tamoxifen; 7-FSH)

Appendix 30 Network plot for multiple pregnancy incorporating risk of bias assessment

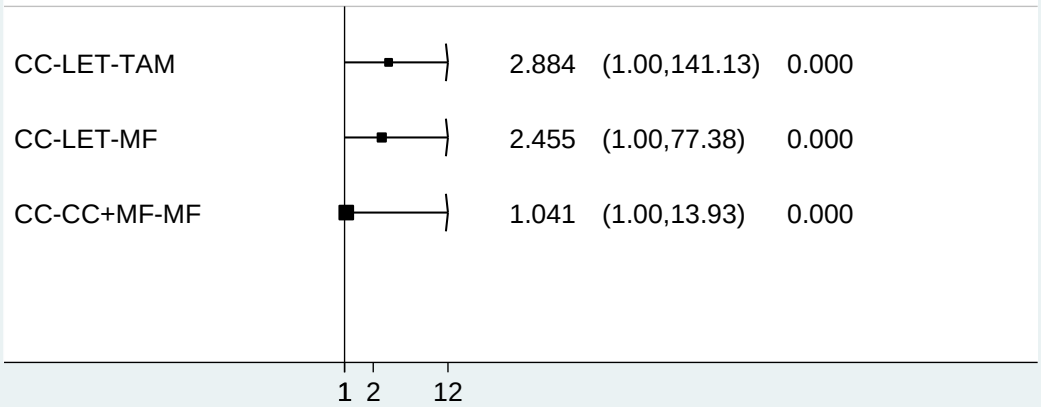
30a. Risk of bias in randomisation



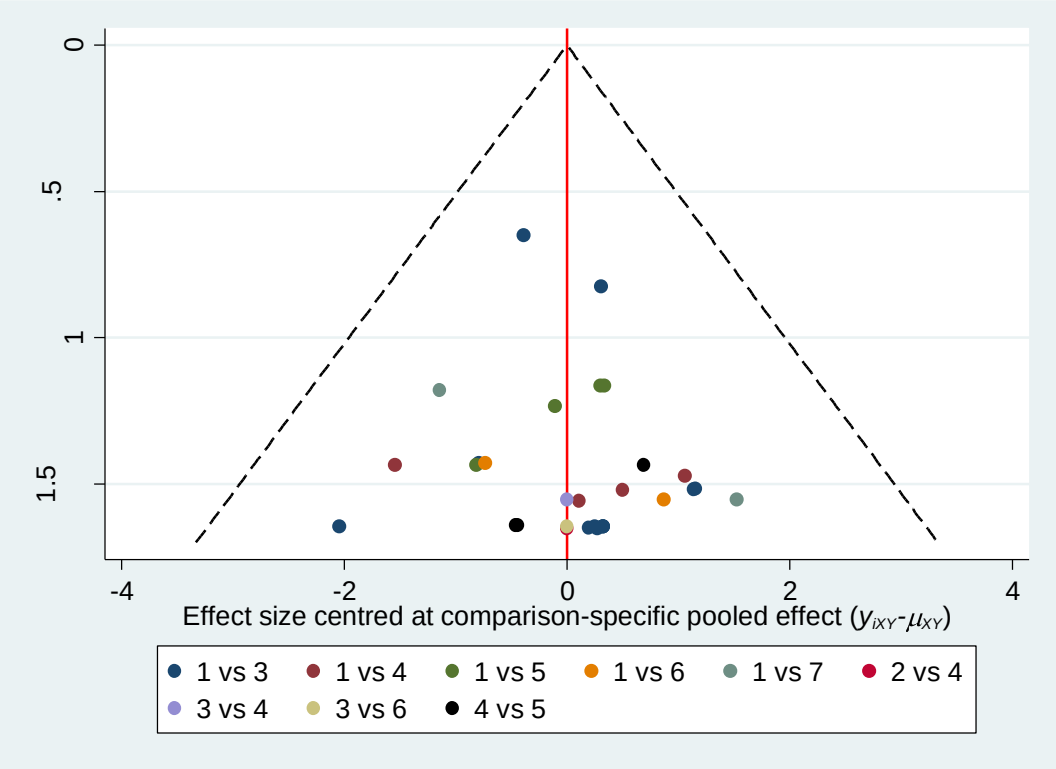
30b. Risk of bias in allocation concealment



Appendix 31 Inconsistency plot for multiple pregnancy

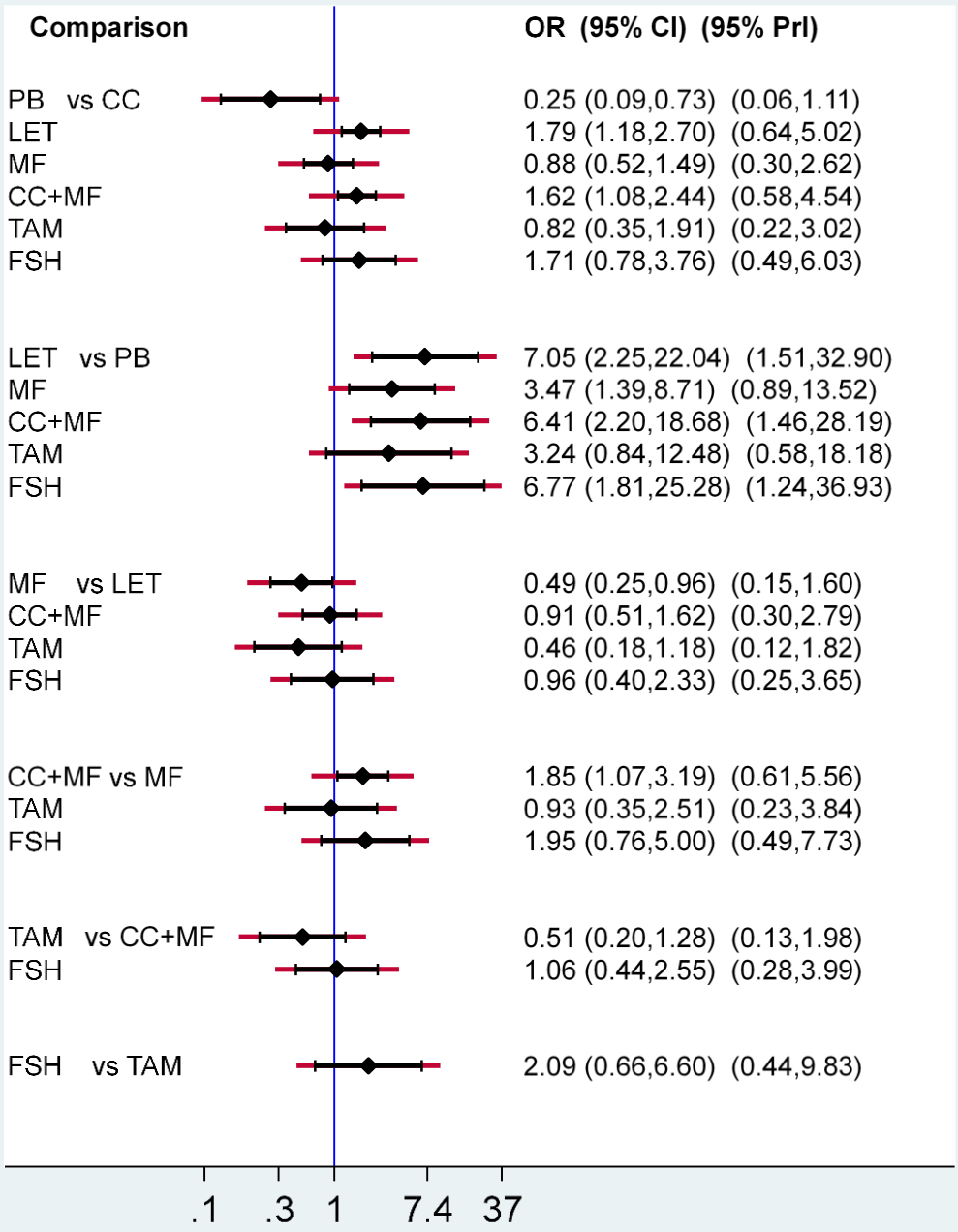


Appendix 32 Comparison-adjusted funnel plot for multiple pregnancy

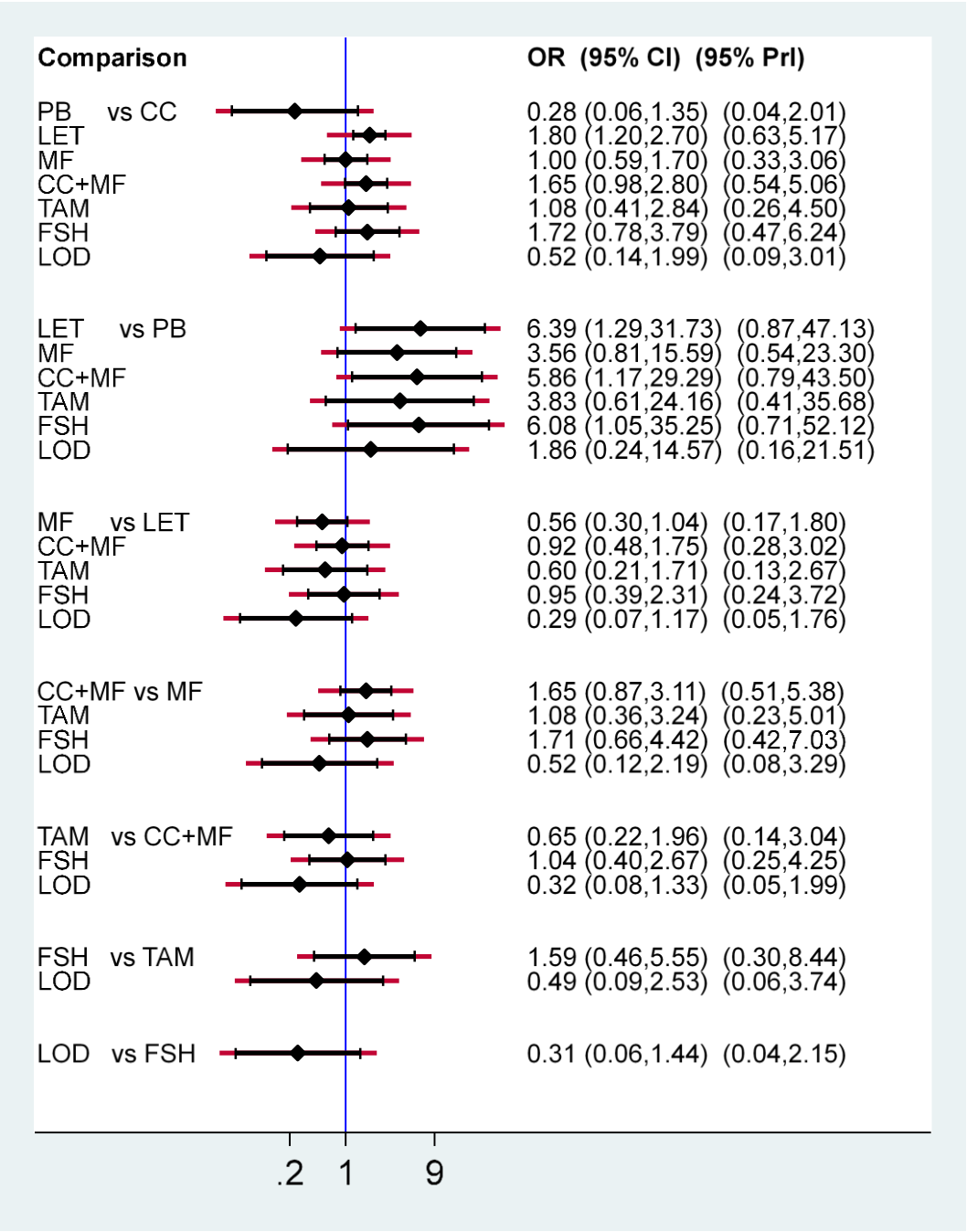


(1-clomiphene; 2-placebo/no treatment; 3-letrozole; 4-metformin; 5-clomiphene plus metformin; 6-tamoxifen; 7-FSH)

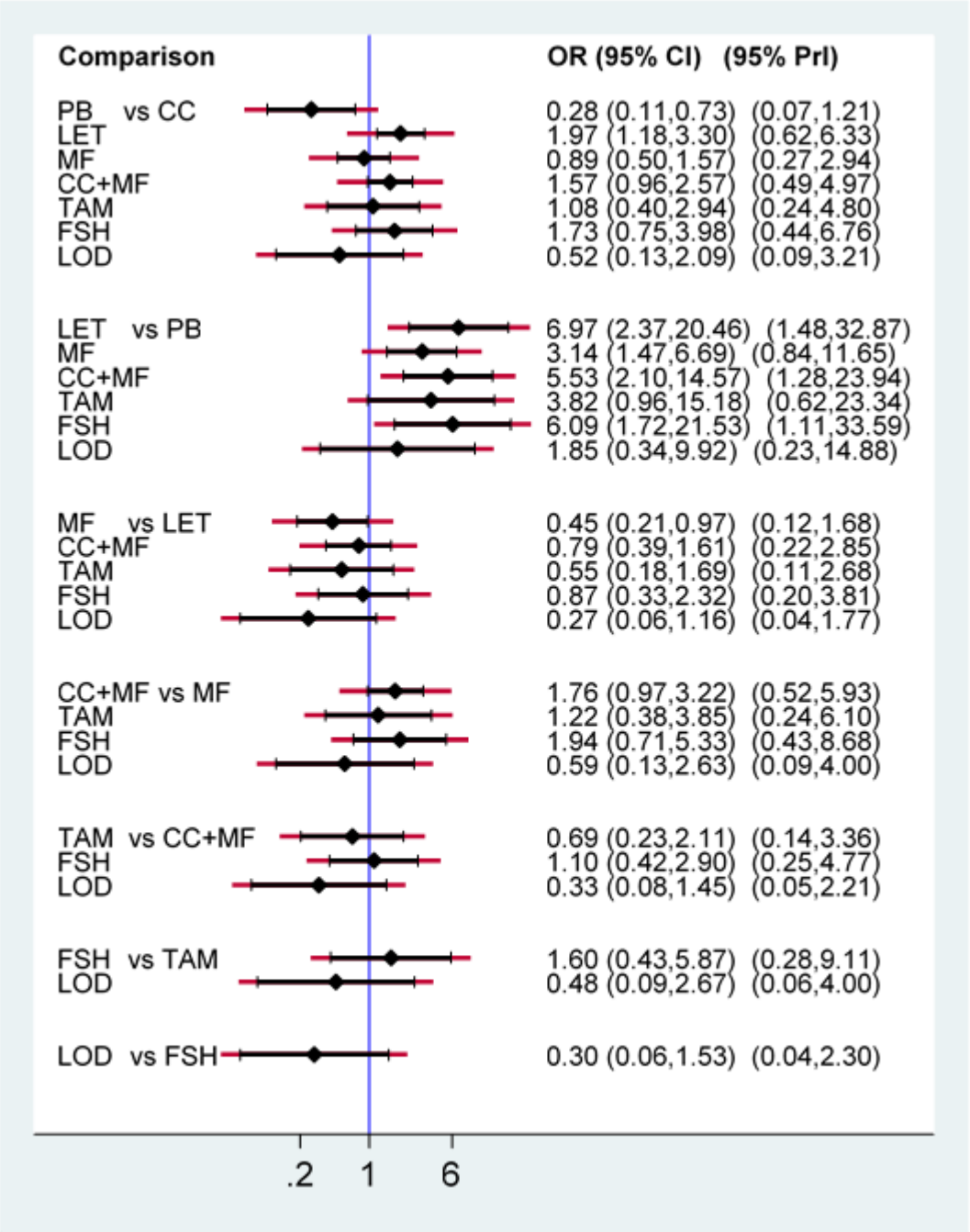
Appendix 33 Sensitivity analysis - RCTs reporting clinical pregnancy



Appendix 34 Sensitivity analysis - RCTs with treatment naïve women



Appendix 35 Sensitivity analysis - RCTs with low risk of randomisation & allocation bias



Appendix 36 Additional discussion

Side effects of the combination of clomiphene and metformin

We have summarised the side effects of the combination of clomiphene and metformin versus clomiphene alone (appendix 37 and 38). Of 19 studies comparing these two interventions, 11 studies reported data on side effects or discontinuation due to side effects. Three studies[1-3] including 714 women reported the number of participants who discontinued treatment due to side effects. In a pairwise meta-analysis for this outcome, we found that more women in the combination group discontinued the treatment due to side effects than women in clomiphene group (OR 2.34, 95% CI 1.04 to 5.30, appendix 37). As the reporting strategies were diverse in different studies, we were not able to perform meta-analyses on overall side effects or any specific types of side effects. As shown in appendix 38, gastrointestinal side effects were more frequent in combined clomiphene-metformin group than clomiphene group.

Quality of evidence and interpretation of data

The overall quality of included studies was moderate in relation to the seven specific domains of the risk of bias assessment. Randomisation and allocation are fundamental requirements for a high quality randomised controlled trial and therefore we integrated these domains in the network plot (appendix 9, 20, 23, 26, 30). Although we excluded quasi-randomised studies in the current systematic review, half of the included randomised controlled trials did not report details of randomisation, and further clarity on this eluded us even after attempts to contact the authors. Specific information about allocation concealment was also unavailable in many of the trials. In multicentre randomised controlled trials with large sample sizes[1 2 4 5], the dropout rates in different interventions varied from 14% to 35%. Many studies with small sample sizes have relatively low or zero dropout rates. Additionally, these studies often claim to have undertaken an intention-to-treat analysis, but it is possible that the authors may have excluded dropouts in their analysis. It is difficult to distinguish those lost to follow up due to adverse events and those for other reasons. CONSORT[6] strongly encourages to report a flow diagram of patient follow up, including reasons for dropouts, however, many included studies failed to do so.

In pairwise meta-analyses, the heterogeneity in comparisons of combined clomiphene-metformin versus clomiphene and letrozole versus clomiphene in all outcomes was low. Therefore, the results of these comparisons in network meta-analysis were robust. By contrast, there was significant heterogeneity in comparisons of clomiphene and metformin. Thus, the results of these comparisons should be interpreted with cautions.

In our network meta-analysis, predictive intervals were used to estimate the effect of a future study. When considering predictive intervals in our network meta-analysis, clomiphene, letrozole, metformin, clomiphene and metformin combined, and follicle stimulating hormone remained superior to placebo. These results indicate that in future studies, these active treatments would remain effective in comparison with placebo/no treatment. Of note, there

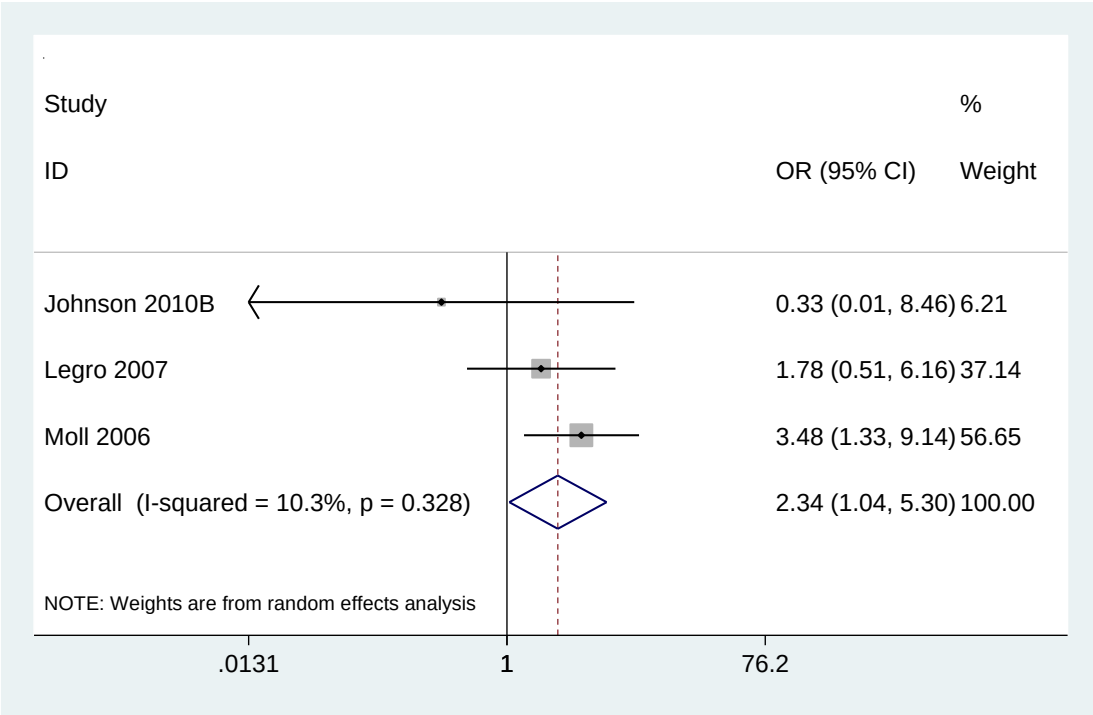
were significant differences between follicle stimulating hormone and metformin/letrozole in terms of multiple pregnancy. However, the wide confidence intervals suggest significant imprecision in the effect size.

According to the rankings, combined clomiphene-metformin, letrozole, and follicle stimulating hormone were the best interventions in terms of pregnancy, live birth and ovulation, while metformin and letrozole were the best interventions in terms of reducing multiple pregnancy rate.

References

1. Legro RS, Barnhart HX, Schlaff WD, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. New England journal of medicine 2007;**356**(6):551-66.
2. Moll E, Bossuyt PM, Korevaar JC, et al. Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial. BMJ (Clinical research ed) 2006;**332**(7556):1485.
3. Johnson NP, Stewart AW, Falkiner J, et al. PCOSMIC: a multi-centre randomized trial in women with PolyCystic Ovary Syndrome evaluating Metformin for Infertility with Clomiphene. Human reproduction 2010;**25**(7):1675-83.
4. Legro RS, Brzyski RG, Diamond MP, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. The New England journal of medicine 2014;**371**(2):119-29.
5. Homburg R, Hendriks ML, Konig TE, et al. Clomifene citrate or low-dose FSH for the first-line treatment of infertile women with anovulation associated with polycystic ovary syndrome: a prospective randomized multinational study. Human reproduction 2012;**27**(2):468-73.
6. Moher D, Schulz KF, Altman D, et al. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. Jama 2001;**285**(15):1987-91.

Appendix 37 Meta-analysis of clomiphene and metformin combined vs clomiphene alone for discontinuation due to side effects.



Boxes and horizontal lines represent ORs and 95% CIs of individual studies. The diamond represents the overall OR and 95% CI (Random-effect model). OR >1 means more women discontinue treatment due to side effect in combined clomiphene-metformin group than clomiphene group.

Appendix 38 Side effects of clomiphene and metformin combined versus clomiphene alone.

Study ID	CC group				CC+Metformin group			
	Women with side effects	Details of side effects	discontinuation due to side effects	Sample size	Women with side effect	Details of side effect	discontinuation due to side effects	Sample size
Abuelghar 2013	6	Flushing: 4; gastrointestinal tract discomfort: 2	NA	32	11	Flushing: 2; gastrointestinal tract discomfort: 5; both: 1; diarrhoea: 3	NA	34
Ayaz 2013	NA	NA	0	21	NA	60% had complained of loss of appetite, 18% had nausea & vomiting	0	21
Basirat 2012	NA	No metformin related side effects.	NA	167	NA	No metformin related side effects.	NA	167
Dasari 2009	NA	NA	0	24	NA	NA[a]	0	16
Johnson 2010B	NA	Gastrointestinal symptoms: 5	1	36	NA	Gastrointestinal symptoms: 11; vasomotor: 1	0	35
Legro 2007	NA	Diarrhoea: 48; dyspepsia: 9; flatulence: 38; nausea: 82; stomach discomfort: 8; vomiting: 28; decreased appetite: 17[b]	4	209	NA	Diarrhoea: 126; dyspepsia: 14; flatulence: 30; nausea: 138; stomach discomfort: 16; vomiting: 72; decreased appetite: 33[b]	7	209
Maged 2015	1	Nausea: 1	NA	40	1	Drowsiness:1	NA	40
Moll 2006	NA	NA	6	114	NA	NA	18	111
Raja 2005	NA	NA	NA	50	6	nausea and diarrhoea: 6	NA	50
Sahin 2004	NA	NA	0	10	NA	NA	0	11
Zain 2009	NA	NA	0	41	NA	NA[c]	0	41

NA: not available.

a. The data of the 16 women in CC+ metformin group were not reported. But the authors reported that of the 25 participants who received metformin along with CC, 80% complained of loss of appetite and 24% had nausea and vomiting. The 25 participants was composed of 16 women in CC + metformin group and 9 women who did not conceive with six cycles of CC alone (given CC + metformin for an additional six cycles) at their request for further treatment.

b. Main gastrointestinal side effects were summarised in this table. This study also reported data on other specific side effects but not the data on overall side effects.

c. The data of CC+metformin group was not reported. Three patients with metformin complained of nausea, dizziness, and headache.

Appendix 39 Congenital malformations in newborns conceived through letrozole vs control.

Study ID	Country	Study design	Congenital malformation	
			Control	Letrozole
Dehbashi 2009[1]	Iran	RCT	CC: 16.6% (1/6) [a]	0% (0/10)
Ray 2012[2]	India	RCT	CC: 0% (0/13)	0% (0/20)
Roy 2012[3]	India	RCT	CC: 0% (0/21)	0% (0/39)
Legro 2014[4]	USA	RCT	CC: 1.5% (1/66) [b]	3.9% (4/102) [c]
Diamond 2015[5]	USA	RCT	CC: 4.3% (3/70) [d]	3.6% (2/56) [e]
Tulandi 2006[6]	Canada	observational	CC/CC+FSH: 4.8(19/397) [f]	Letrozole/Letrozole+FSH: 2.4% (14/514) [g]
Forman 2007[7]	Canada	observational	2.6% (7/271) [h]	0% (0/94)
Sharma 2014[8]	India	observational	CC:4.0% (10/251) [I]; Natural conception: 2.9% (5/171)[k]	2.5% (5/201) [j]
Wu 2016[9]	China	RCT	Berberine: 0% (0/48)	Letrozole alone: 1.2%(1/84)[l]; Letrozole+Berberine: 1.2%(1/81)[m]
Tatsumi 2016[10]	Japan	observational	Natural cycle IVF/ICSI: 1.9% (44/2287)[n]	Letrozole + IVF/ICSI: 2.2%(15/694)[o]

Details of congenital malformations in these studies:

a. Meningomyelocele.

b. Atrial septal defect (ASD), ventricular septal defect (VSD), and pulmonary stenosis.

c. 1) Cerebral palsy with arrested hydrocephalus with polycythemia and neutropenia; 2) imperforate anus with perineal fistula and spina bifida with a tethered spinal cord; 3) right hemimegalencephaly, and dysgenesis of the left frontal and temporal lobes but no hydrocephalus; 4) large cardiac VSD requiring surgical repair.

d. 1) Aortic arch hypoplasia; 2) Congenital hypothyroidism; 3) Renal duplicated right collecting system and ureterocele.

e. 1) Hypospadias; 2)Right facial hemangioma; Biventricular hypertrophy; Bifid uvula; Small cataracts bilaterally; Widening of the corneal horizontal diameter.

f. Major malformations (12 cases): 1) VSD (4 cases); 2) Transposition of great vessels; 3) Atresia of pulmonary valve and right ventricle; 4) Pulmonary valve atresia; 5) Pyelectasis; 6) Omphalocele; 7) Cleft palate; 8) Spinal muscular atrophy; 9) Down's syndrome.
Minor malformations (7 cases): 1) Preauricular skin tag (2 cases); 2) Horseshoe kidney; 3) Polydactyly (3 cases); 4) Unspecific hypotonia.
g. Major malformations (6 cases): 1) VSD; 2) Esophageal atresia; 3) Cleft palate; 4) Trisomy 18; 5) Down's syndrome; 6) Potter's syndrome.
Minor malformations (8 cases): 1) Preauricular skin tag; 2) Congenital ptosis; 3) Plagiocephaly; 4) Hydrocele; 5) Hypospadia; 6) Polydactyly; 7) Syndactyly (2nd and 3rd toes); 8) Umbilical and inguinal hernias.
h. 7 cases with major malformations but details not reported.
i. 1) Patent ductus arteriosus (2 cases) and; 2) total anomalous venous connection; 3) Hypospadias (3 cases); 4) bilateral congenital talipus equino varus; 5) duplication of urethra; 6) cleft lip & palate; 7)inguinal hernia; 8)neural tube defect; 9) Down's syndrome (2 cases). Three babies with congenital heart disease were excluded from the analysis by the authors as they were born to diabetic mothers.
j. 1) Combined ventricular and ASD; 2) paraumbilical hernia; 3) congenital deafness; 4) congenital talipus equino varus; 5) albinism.
k. 1) VSD; 2) Congenital talipus equino varus; 3)cleft lip; 4) imperforate anus; 5)polydactyly.
l. Hydrocephalus.
m. Major VSD and pulmonary stenosis.
n. Major anomalies (34 cases): including chromosomal abnormalities (11 cases), cardiovascular abnormalities (13 cases) and musculoskeletal abnormalities (1 case).
o. Major anomalies (13 cases): 1) ASD,VSD; 2)ASD,VSD, Down's syndrome; 3) Cleft lip without cleft palate; 4) Congenital hydronephrosis; 5) Diaphragmatic hernia; 6) Duodenal atresia; 7) Endocardial cushion defect, down syndrome; 8) Hypospadias; 9) Trisomy 18; 10) VSD (2 cases); 11)VSD, down syndrome; 12) Anencephalus.

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